#17

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,236,952

Attn: Box Patent Ext.

Inventors: Bernauer, et al.

Issue Date: August 17, 1993

For: CATECHOL DERIVATIVES

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
February 26, 1998

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 35 U.S.C. § 156, Hoffmann-La Roche Inc. ("ROCHE"), a corporation organized under the laws of the State of New Jersey and owner of U.S. Patent No. 5,236,952, by assignment recorded on April 27, 1987 at reel 4702, frames 962 and 963, submits this Application for extension of its term.

Applicant seeks extension of the term of U.S. Patent No. 5,236,952 for one (1) year and one hundred and sixty five (165) days, from August 17, 2010 to and including January 29, 2012 and certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

The information contained in this document and its Exhibits is provided in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and is listed in the manner set forth in § 1.740.

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

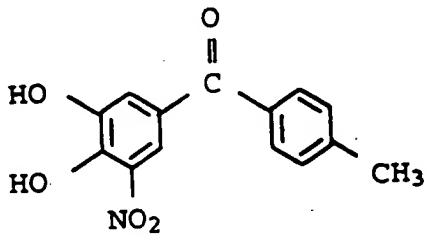
The approved product, having the trademark Tasmar® Tablets, contains tolcapone as the sole active ingredient. The product is approved to be supplied in tablets, each tablet containing 100 mg or 200 mg tolcapone. Tolcapone is an inhibitor of catechol-O-methyltransferase (COMT). For the core, the inactive ingredients present are lactose monohydrate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc and magnesium stearate. For the film coating, the inactive ingredients present are hydroxypropyl methyl cellulose, titanium dioxide, talc, ethylcellulose, triacetin and sodium lauryl sulfate, wiht the following dye systems: 100 mg-yellow and red iron oxide; 200 mg-red iron oxide. (Exhibit 1).

"Tolcapone" is the non-proprietary name approved by the USAN council for the active ingredient of Tasmar.

Tolcapone, also known as Ro 40-7592, has the following chemical name:

1. 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone

Tolcapone has the structural formula:



The approved therapy for the approved product is always as an adjunct to levodopa/carbidopa therapy.

The term "approved product" is defined in 35 U.S.C. § 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. § 156(f)(1)(A) to comprise a "drug product" which is described in 35 U.S.C. § 156(f) (2) to include "the active ingredient of a new drug . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." The approved product subject to this Application, Tasmar tablets, thus includes tolcapone, and any salts and esters thereof, as its active ingredient, as a single entity or in combination with another active ingredient.

(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 301 et seq.

(3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

Tasmar Tablets were approved by the Food and Drug Administration ("FDA") for commercial marketing or use under Section 505 of the FD&C Act on January 29, 1998 (Exhibit 2).

(4) In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The sole active ingredient in the approved product is tolcapone, which active ingredient has not been previously approved for commercial marketing or use under the FD&C Act, The Public Health Services Act or the Virus-Serum-Toxin Act.

(5) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to § 1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is March 30, 1998.

(6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of the Inventor, The Patent Number, The Date Of Issue, And The Date of Expiration

The complete identification of the patent for which an extension is being sought is:

Inventors:	Karl Bernauer Janos Borgulya Hans Bruderer Mosé DaPrada Gerhard Zürcher
Patent No:	5,236,952
Issue Date:	August 17, 1993
Expiration Date:	August 17, 2010 (without extension)

(7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 5,236,952 is attached as Exhibit 3.

(8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In the Patent

No disclaimer, or reexamination certificate has been issued for U.S. Patent No. 5,236,952. A copy of a Certificate of Correction dated May 9, 1995 that issued for U.S. Patent No. 5,236,952 is attached as Exhibit 4. A copy of a receipt of maintenance fee payment for U.S. Patent No. 5,236,952, received by applicant on February 7, 1997 is attached as Exhibit 5.

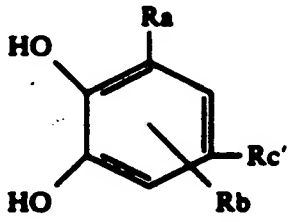
U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

(9) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which Each Applicable Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

United States Patent No. 5,236,952 claims the approved product or a method of using the approved product in claims 1, 2, 3, 4, 5, 8, 11, 14, 16, 19, 20, 21 and 22.

Claim 1, in an edited form, reads as follows:

1. A compound of the formula



Ib

wherein Ra is nitro ..., Rb is hydrogen ..., Rc' is the group CO-R^{11} wherein R^{11} is a phenyl group optionally mono- or disubstituted by ... lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof.

When Ra is nitro, Rb is hydrogen, and R^{11} is a phenyl monsubstituted by methyl (lower alkyl), Claim 1 reads on the approved product.

Claim 2 reads as follows:

2. A compound, according to claim 1, wherein Rb is situated in the p-position to Ra.

Accordingly, Claim 2 reads on the approved product.

Claim 3 reads as follows:

3. A compound, according to claim 2, wherein Ra is nitro.

Accordingly, Claim 3 reads on the approved product.

Claim 4 reads as follows:

4. A compound, according to claim 3, wherein Rb is hydrogen, chlorine or fluorine.

When Rb is hydrogen, Claim 4 reads on the approved product.

Claim 5 reads as follows:

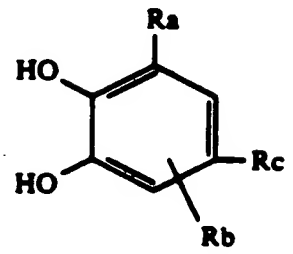
5. A compound, according to claim 4, wherein Rb is hydrogen.

Accordingly, Claim 5 reads on the approved product.

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

Claim 8 reads as follows:

8. A pharmaceutical composition comprising a compound of the formula

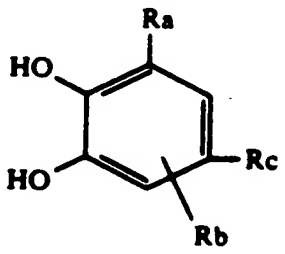


wherein Ra is nitro ..., Rb is hydrogen ..., Rc' is the group CO-R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by ... lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

When Ra is nitro, Rb is hydrogen, and R^1 is a phenyl monsubstituted by methyl (lower alkyl) and the inert carrier material is any of the inactive ingredients described in item 1, Claim 8 reads on the approved product.

Claim 11 reads as follows:

11. A pharmaceutical composition comprising L-dopa, peripheral decarboxylase inhibitor, a compound of the formula



wherein Ra is nitro ..., Rb is hydrogen ..., Rc' is the group CO-R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by ... lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier material.

When the compound or its ester or salt is administered as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, and when Ra is nitro, Rb is hydrogen, and R^1 is a phenyl monsubstituted by methyl (lower alkyl) and the inert carrier material is any of the inactive ingredients described in item 1, Claim 11 reads on the approved product.

Claim 14, as corrected as per the enclosed Certificate of Correction dated May 9, 1995, reads as follows:

14. A compound according to claim 1, wherein said compound is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

Accordingly, Claim 14 reads on the approved product.

Claim 15 reads as follows:

15. A pharmaceutical composition according to claim 8, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

Accordingly, Claim 15 reads on the approved product.

U.S. Patent No. 5,236,952
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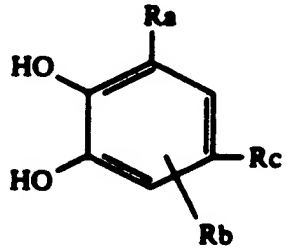
Claim 16 reads as follows:

16. A pharmaceutical composition according to claim 11, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

When the compound is administered as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, Claim 16 reads on the approved product.

Claim 19 reads as follows:

19. A pharmaceutical composition for treating Parkinson's disease comprising L-dopa, a peripheral decarboxylase inhibitor, a compound of the formula



Ia

wherein Ra is nitro ..., Rb is hydrogen ..., Rc' is the group CO-R^1 wherein
R^1 is a phenyl group optionally mono- or disubstituted by ... lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

When the compound or its ester or salt is administered for treating Parkinson's disease as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, and

when Ra is nitro, Rb is hydrogen, and R^1 is a phenyl monsubstituted by methyl (lower alkyl) and the inert carrier material is any one of the inactive ingredients described above, Claim 19 reads on the approved product.

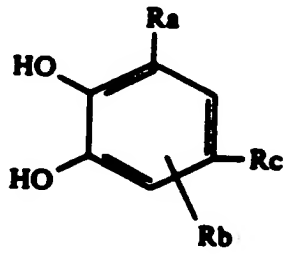
Claim 20 reads as follows:

20. A pharmaceutical composition according to claim 19, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

When the compound is administered for treating Parkinson's disease as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, Claim 20 reads on the approved product.

Claim 21 reads as follows:

21. A pharmaceutical composition for inhibiting catechol-O-methyl-transferase, said composition comprising a catechol-O-methyl transferase inhibiting amount of a compound of the formula



Ia

wherein Ra is nitro ..., Rb is hydrogen ..., Rc is the group CO-R^1 wherein
R^1 is a phenyl group optionally mono- or disubstituted by ... lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

When the compound or its ester or salt inhibits catechol-O-methyl-transferase and is administered as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, and when Ra is nitro, Rb is hydrogen, and R^1 is a phenyl monsubstituted by methyl (lower alkyl) and the inert carrier material is any one of the inactive ingredients described above, Claim 21 reads on the approved product.

Claim 22 reads as follows:

22. A pharmaceutical composition according to claim 8, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

When the compound inhibits catechol-O-methyl-transferase and is administered as an adjunct to L-dopa such as levadopa and peripheral decarboxylase inhibitor such as carbidopa, Claim 22 reads on the approved product.

As demonstrated above, Claims 1, 2, 3, 4, 5, 8, 11, 14, 15, 16, 19, 20, 21, and 22 read on the approved product.

(10) A Statement, Beginning on a New Page, of The Relevant Dates And Information Pursuant To 35 U.S.C. 156(g) In Order To Enable The Secretary Of Health and Human Services or the Secretary of Agriculture, As Appropriate, To Determine the Applicable Regulatory Review Period as Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) or a Product License Application (PLA) Was Initially Submitted And The NDA or PLA Number And The Date On which The NDA Was Approved or the Product License Issued

a)	Effective date of the investigational new drug application (IND) and IND number.	November 28, 1990 (Exhibit 6) IND No. 35,698
b)	Date on which a New Drug Application (NDA) was initially submitted and NDA number:	June 3, 1996 (Exhibit 7) NDA No. 20-697
c)	Date on which NDA was approved:	January 29, 1998 (Exhibit 2)[1]

[1] An FDA letter dated January 29, 1998 approving Tasmar Tablets is provided as Exhibit 2. On January 30, 1998 the FDA provided an amended page 1 of the January 29 approval letter which differs from the January 29 version in that it contains one additional sentence concerning product expiration. A copy of this amended page is also provided with Exhibit 2.

(11) A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of significant activities undertaken by applicants during the regulatory review period with respect to the approved product is attached as Exhibit 8. This Exhibit specifically is directed to the communications between applicant and the FDA. The Exhibit provides, for a given correspondence, the nature of the correspondence including a brief summary of its subject matter, and the date of the correspondence. For convenience, the chronology is divided into a Testing Phase and an Application Phase.

If necessary, applicant reserves the right to supplement its chronology in Exhibit 8 with materials from which it was derived and other evidence related to applicant's conduct in obtaining the approval of Tasmar Tablets, See, e.g., 21 C.F.R. § 60.32.

(12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Eligibility

Under the law and in the opinion of Applicant, U.S. Patent No. 5,236,952 is eligible for an extension under 35 U.S.C. § 156.

In particular, 35 U.S.C. § 156(a) in its relevant parts, provide that the term of a patent shall be extended if the following requirements are satisfied: (1) the patent claims a product, a method of using a product or a method of manufacturing a product; (2) the term of the patent has not expired before an application for extension is submitted; (3) the term of the patent has never been extended; (4) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (5) the product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(a) before its commercial marketing or use; and (6) the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 5,236,952 claims a product, a method of using a product or a method of manufacturing a product.

2. The term of U.S. Patent No. 5,236,952 presently will expire on August 17, 2010 and thus, the patent has not expired before submission of this Application.

3. The term of U.S. Patent No. 5,236,952 has never been extended under 35 U.S.C. § 156.

4. This Application is submitted by ROCHE, the owner of record of U.S. Patent No. 5,236,952. This Application is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 within the sixty (60) day period beginning on January 29, 1998 and ending March 30, 1998. The product received permission for marketing or use under FD&C Act. This Application contains the information required under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

5. The product was subject to a regulatory review period under Sections 505 of the FD&C Act before its commercial marketing or use, as evidenced by the chronology (Exhibit 8) and the Letter of Approval from the FDA, dated January 29, 1998 (Exhibit 2).

6. The permission for the commercial marketing or use of the approved product, after the regulatory review period is the first permitted commercial marketing or use of a product having tolcapone in any form as its active ingredient, under the provisions of the FD&C Act under which such regulatory review period occurred. This is confirmed by the absence of any approved drug application for the active ingredient of the approved product in any form prior to January 29, 1998.

Accordingly, U.S. Patent No. 5,236,952 satisfies the requirements for an extension under 35 U.S.C. § 156.

Length

Under the law and in the opinion of Applicant, the term of U.S. patent No. 5,236,952 should be extended for a period of one (1) year and one hundred and sixty five (165) days, from August 17, 2010 to and including January 29, 2012.

This extension was determined on the following basis:

Testing Phase (37 C.F.R. § 1.775(c) (1))

For the approved product, that portion of the regulatory review period as defined in 35 U.S.C. 156 (g) (1) (B) (i) ("Testing Phase") commenced on November 28, 1990 and ended on June 3, 1996, which is 2014 days.

Application Phase (37 C.F.R. § 1.775(c) (2))

For the approved product, that portion of the regulatory review period as defined under 35 U.S.C. 156 (g) (1) (B) (ii) ("Application Phase") commenced on June 3, 1996 and ended on January 29, 1998, which is six hundred and five (605) days.

Regulatory Review Period (37 C.F.R. § 1.775(c))

As defined in 35 U.S.C. 156 (g) (1) (B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of two thousand six hundred and nineteen (2619) days.

Reduction for Review Prior to the Issue of The Patent (37 C.F.R. § 1.775 (d) (1) (i))

The applicable regulatory review period is reduced by that period of review occurring before and on the date the patent issued.

U.S. Patent No. 5,236,952 (Exhibit 3) issued August 17, 1993 and the effective date of the IND was November 28, 1990. Accordingly, a reduction of nine nundred and ninety three (993) days for review prior to the issue of the patent applies.

Thus, taking into account the reduction of nine hundred and ninety three (993) days for review prior to the issue of the patent, the applicable regulatory period is one thousand six hundred and twenty six (1626) days.

Due Diligence Reduction to Regulatory Review Period (37 C.F.R. § 1.775 (d) (1) (ii))

Under 35 U.S.C. § 156(c) (1), the Testing Phase and Application Phase of the regulatory review period are reduced by the period during which the applicant for the patent extension, in the regulatory review period, did not act with due diligence. In the opinion of the Applicant and illustrated by the chronology in Exhibit 8, it acted with due diligence during both periods of time. Thus, there is

no reduction in the regulatory review period because of lack of due diligence. In a correspondence dated May 30, 1991, the FDA requested, prior to initiation of Phase II clinical trials, additional non-clinical characterization of tolcapone when administered with Sinemet® (carbidopa/levadopa). As outlined in Exhibit 8, applicant diligently performed the requested characterization and continuously provided results to the FDA. The FDA approved initiation of Phase II clinical trials on March 1, 1993. In addition, as outlined in Exhibit 8, during this period of time, applicant continued to diligently conduct Phase I clinical trials.

One-Half Testing Phase Reduction (37 C.F.R. § 1.775 (d) (1) (iii))

Under 35 U.S.C. § 156(c) (2), the one thousand six hundred and twenty six (1626) day regulatory review period is reduced by one-half of the two thousand and fourteen (2014) day Testing Phase. One-half of the Testing Phase is one thousand and seven (1007) days. Thus, the one thousand six hundred and twenty six (1626) day regulatory review period is reduced by one thousand and seven (1007) days leaving a final revised regulatory review period of six hundred and nineteen (619) days.

Fourteen Year Cap (37 C.F.R. § 1.775 (d) (2) - (4)

Under 35 U.S.C. § 156(c) (3) should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceed fourteen (14) years, the period of extension is reduced so that the total of both such periods does not exceed fourteen (14) years. In applying section 156(c) (3), the final revised regulatory review period as calculated above six hundred and nineteen (619) days is added onto the end of the original term of the patent August 17, 2010 resulting in a date of April 27, 2012. Alternatively, fourteen (14) years is added to the NDA approval date (January 29, 1998) resulting in a date of January 29, 2012. The earlier of the above two dates, January 29, 2012, is selected.

Two and Five Year Extension Limits (37 C.F.R. § 1.775 (d) (5) & (6)

A patent issued after September 24, 1984 is limited to a maximum extension of five years.

U.S. Patent No. 5,236,952 (Exhibit 3) issued on August 17, 1993. Accordingly, the patent is eligible for an extension of up to five years.

As set forth above, the term of U.S. Patent No. 5,236,952 is eligible for a extension of one (1) year and one hundred and sixty five (165) days from August 17, 2010 to and including January 29, 2012.

(13) A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

(14) The Prescribed Fee for Receiving and Acting Upon the Application for Extension

Applicant encloses (in duplicate) a transmittal letter requesting the amount of $1060.00 be charged to Account No. 08-2525.

(15) The Name, Address and Telephone Number Of The Person to Whom Inquiries and Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

George W. Johnston
Hoffmann-La Roche Inc.
Patent Law Department
340 Kingsland Street
Nutley, New Jersey 07110

Please direct all telephone calls to:

Robert A. Silverman
(937) 235-2863

(16) A Duplicate of These Application Papers, Certified As Such

A certified duplicate is enclosed.

(17) An Oath or Declaration As Set Forth In Paragraph (b) of 37 C.F.R. § 1.740

Applicant attaches a declaration as set forth in 37 C.F.R. § 1.740(b), signed by an officer of Roche, the owner of record of U.S. Patent No. 5,236,952, who is authorized to practice before the Patent and Trademark Office and who has general authority to act on ROCHE's behalf in patent matters.

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

Request for Extension

Having included in this Application all of the requisite information under 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant requests (i) an extension of U.S. Patent No. 5,236,952 for one (1) year and one hundred and sixty five (166) days from August 17, 2010 to and including January 29, 2012, by reason of its claiming the approved product and (ii) certification that it is entitled to the rights derived from this patent as set forth in 35 U.S.C. § 156(b).

Respectfully submitted,

HOFFMANN-LA ROCHE INC.

By: _____

Robert A. Silverman
Name (Print)

Senior Counsel
Title

Registration No. 35682

February 26, 1998
Date

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 U.S.C. § 156 including its exhibits is being submitted as duplicate originals.

By: _____
Robert A. Silverman
Registration No. 35682

Date: February 26, 1998

43092

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,236,952 Attn: Box Patent Ext.

Inventors: Bernauer et al.

Issue Date: August 17, 1993

For: **CATECHOL DERIVATIVES**

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
February 26, 1998

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith are the following: a) Application for Extension of Patent Term Under 35 U.S.C. §156 with Exhibits (separately bound) and b) Declaration and Power of Attorney for Application for Extension of Patent Term under 35 U.S.C. §156, for U.S. Patent No. 5,236,952. The Application is being submitted in duplicate, and the undersigned certifies that each copy of the attached Application is a duplicate original. In addition, three courtesy copies of all papers filed are being provided for the convenience of the Assistant Commissioner.

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

Please charge Deposit Account No. 08-2525 in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

A duplicate copy of this cover sheet is enclosed.

Respectfully submitted,

Attorney for Applicant(s)
Robert A. Silverman
(Reg. No. 35682)
340 Kingsland Street
Nutley, New Jersey 07110-1199
Telephone: (201) 235-2863
Telefax: (201) 235-2363

43090

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,236,952 Attn: Box Patent Ext.

Inventors: Bernauer et al.

Issue Date: August 17, 1993

For: **CATECHOL DERIVATIVES**

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

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DEPOSIT ACCOUNT
NO. 08-2525
OUR ORDER NO. 1550

U.S. Patent No. 5,236,952
Issue Date: August 17, 1993

Please charge Deposit Account No. 08-2525 in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

A duplicate copy of this cover sheet is enclosed.

Respectfully submitted,

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43090

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,236,952

Inventors: Bernauer, et al.

Issue Date: August 17, 1993

For: CATECHOL DERIVATIVES

Attn: Box Patent Ext.

DECLARATION AND POWER OF ATTORNEY FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Nutley, New Jersey 07110
February 26, 1998

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, George W. Johnston, a Vice President of Hoffmann-La Roche Inc. ("ROCHE"), which submits the attached Application for Extension of Patent Term Under 35 U.S.C. § 156, of the same date as this Declaration, declare that:

(1) ROCHE is the owner of record of U.S. Patent No. 5,236,952 and I am authorized to obligate ROCHE;

(2) I am a patent attorney authorized to practice before the Patent and Trademark Office and have general authority from ROCHE to act on its behalf in patent matters;

(3) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 5,236,952 pursuant to 35 U.S.C. § 156 and 37 C.F.R. §1.710 et seq;

(4) I believe this patent is subject to extension under 35 U.S.C. § 156 and 37 C.F.R. §1.710;

(5) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(6) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156, and more particularly, in 37 C.F.R. §1.720.

I hereby appoint the following attorneys as agents for ROCHE under 35 U.S.C. § 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith: George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542), Patricia S. Rocha-Tramaloni (Reg. No. 31054), and Robert A. Silverman (Reg. No. 35,682).

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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application or any extension of U.S. Patent No. 5,236,952.

Respectfully submitted,
HOFFMANN-LA ROCHE INC.
By: George W. Johnston
George W. Johnston
Vice President

Date: February 26, 1998

55464

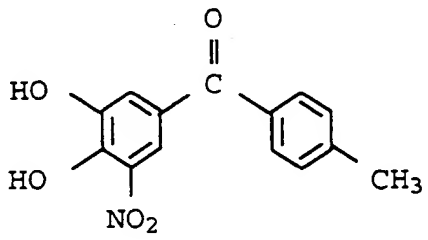
Exhibit 1

(Roche Hexagon)

TASMAR®
(tolcapone)
TABLETS

DESCRIPTION: TASMAR® is available as tablets containing 100 mg or 200 mg tolcapone.

Tolcapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. It is a yellow, odorless, non-hygroscopic, crystalline compound with a relative molecular mass of 273.25. The chemical name of tolcapone is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone. Its empirical formula is $C_{14}H_{11}NO_5$ and its structural formula is:



Inactive ingredients: Core: lactose monohydrate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc and magnesium stearate. Film coating: hydroxypropyl methyl cellulose, titanium dioxide, talc, ethylcellulose, triacetin and sodium lauryl sulfate, with the following dye systems: 100 mg—yellow and red iron oxide; 200 mg—red iron oxide.

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** Tolcapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs. The highest activities are in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

The precise mechanism of action of tolcapone is unknown, but it is believed to be related to its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When tolcapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that these sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading

to greater effects on the signs and symptoms of Parkinson's disease in patients as well as increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa. Tolcapone enters the CNS to a minimal extent, but has been shown to inhibit central COMT activity in animals.

Pharmacodynamics: *COMT Activity in Erythrocytes:* Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. The inhibition is closely related to plasma tolcapone concentrations. With a 200 mg single dose of tolcapone, maximum inhibition of erythrocyte COMT activity is on average greater than 80%. During multiple dosing with tolcapone (200 mg tid), erythrocyte COMT inhibition at trough tolcapone blood concentrations is 30% to 45%.

Effect on the Pharmacokinetics of Levodopa and its Metabolites: When tolcapone is administered together with levodopa/carbidopa, it increases the relative bioavailability (AUC) of levodopa by approximately twofold. This is due to a decrease in levodopa clearance resulting in a prolongation of the terminal elimination half-life of levodopa (from approximately 2 hours to 3.5 hours). In general, the average peak levodopa plasma concentration (C_{max}) and the time of its occurrence (T_{max}) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment. Studies in healthy volunteers and Parkinson's disease patients have confirmed that the maximal effect occurs with 100 mg to 200 mg tolcapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by tolcapone when given with levodopa/carbidopa.

Population pharmacokinetic analyses in patients with Parkinson's disease have shown the same effects of tolcapone on levodopa plasma concentrations that occur in healthy volunteers.

Pharmacokinetics of Tolcapone: Tolcapone pharmacokinetics are linear over the dose range of 50 mg to 400 mg, independent of levodopa/carbidopa coadministration. The elimination half-life of tolcapone is 2 to 3 hours and there is no significant accumulation. With tid dosing of 100 mg or 200 mg, C_{max} is approximately 3 μg/mL and 6 μg/mL, respectively.

Absorption: Tolcapone is rapidly absorbed, with a T_{max} of approximately 2 hours. The absolute bioavailability following oral administration is about 65%. Food given within 1 hour before and 2 hours after dosing of tolcapone decreases the relative bioavailability by 10% to 20% (see DOSAGE AND ADMINISTRATION).

Distribution: The steady-state volume of distribution of tolcapone is small (9 L). Tolcapone does not distribute widely into tissues due to its high plasma protein binding. The plasma protein binding of tolcapone is >99.9% over the concentration range of 0.32 to 210 μg/mL. In vitro experiments have shown that tolcapone binds mainly to serum albumin.

Metabolism and Elimination: Tolcapone is almost completely metabolized prior to excretion, with only a very small amount (0.5% of dose) found unchanged in urine. The main metabolic pathway of tolcapone is glucuronidation; the glucuronide conjugate is inactive. In addition, the compound is methylated by COMT to 3-*O*-methyl-tolcapone. Tolcapone is metabolized to a primary alcohol (hydroxylation of the methyl group), which is subsequently oxidized to the

carboxylic acid. In vitro experiments suggest that the oxidation may be catalyzed by cytochrome P450 3A4 and P450 2A6. The reduction to an amine and subsequent *N*-acetylation occur to a minor extent. After oral administration of a ^{14}C-labeled dose of tolcapone, 60% of labeled material is excreted in urine and 40% in feces.

Tolcapone is a low-extraction ratio drug (extraction ratio = 0.15) with a moderate systemic clearance of about 7L/h.

Special Populations: Tolcapone pharmacokinetics are independent of sex, age, body weight, and race (Japanese, Black and Caucasian). Polymorphic metabolism is unlikely based on the metabolic pathways involved.

Hepatic Impairment: A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. In patients with moderate cirrhotic liver disease (Child-Pugh Class B), however, clearance and volume of distribution of unbound tolcapone was reduced by almost 50%. This reduction may increase the average concentration of unbound drug by twofold (see DOSAGE AND ADMINISTRATION).

Renal Impairment: The pharmacokinetics of tolcapone have not been investigated in a specific renal impairment study. However, the relationship of renal function and tolcapone pharmacokinetics has been investigated using population pharmacokinetics during clinical trials. The data of more than 400 patients have confirmed that over a wide range of creatinine clearance values (30 mL/min to 130 mL/min) the pharmacokinetics of tolcapone are unaffected by renal function. This could be explained by the fact that only a negligible amount of unchanged tolcapone (0.5%) is excreted in the urine. The glucuronide conjugate of tolcapone is mainly excreted in the urine but is also excreted in the bile. Accumulation of this stable and inactive metabolite should not present a risk in renally impaired patients with creatinine clearance above 25 mL/min (see DOSAGE AND ADMINISTRATION). Given the very high protein binding of tolcapone, no significant removal of the drug by hemodialysis would be expected.

Drug Interactions: See PRECAUTIONS: *Drug Interactions.*

Clinical Studies: The effectiveness of TASMAR as an adjunct to levodopa in the treatment of Parkinson's disease was established in three multicenter randomized controlled trials of 13 to 26 weeks duration, supported by four 6-week trials whose results were consistent with those of the longer trials. In two of the longer trials, tolcapone was evaluated in patients whose Parkinson's disease was characterized by deterioration in their response to levodopa at the end of a dosing interval (so-called fluctuating patients with wearing-off phenomena). In the remaining trial, tolcapone was evaluated in patients whose response to levodopa was relatively stable (so-called non-fluctuators).

Fluctuating Patients: In two 3-month trials, patients with documented episodes of wearing-off phenomena, despite optimum levodopa therapy, were randomized to receive placebo, tolcapone 100 mg tid or 200 mg tid. The formal double-blind portion of the trial was 3 months long, and the primary outcome was a comparison between treatments in the change from baseline in the amount of time spent "On" (a period of relatively good functioning) and "Off" (a period of

relatively poor functioning). Patients recorded periodically, throughout the duration of the trial, the time spent in each of these states.

In addition to the primary outcome, patients were also assessed using sub-parts of the Unified Parkinson's Disease Rating Scale (UPDRS), a frequently used multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor function (Part III), complications of therapy (Part IV), and disease staging (Part V & VI); an Investigator's Global Assessment of Change (IGA), a subjective scale designed to assess global functioning in 5 areas of Parkinson's disease; the Sickness Impact Profile (SIP), a multi-item scale in 12 domains designed to assess the patient's functioning in multiple areas; and the change in daily levodopa/carbidopa dose.

In one of the studies, 202 patients were randomized in 11 centers in the United States and Canada. In this trial, all patients were receiving concomitant levodopa and carbidopa. In the second trial, 177 patients were randomized in 24 centers in Europe. In this trial, all patients were receiving concomitant levodopa and benserazide.

The following tables display the results of these 2 trials:

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Table 1. US/Canadian Fluctuator Study

	Baseline (hrs)	Change from Baseline at Month 3 (hrs)	p-value*
Primary Measure			
*Hours of Wake Time "Off"***			
placebo	6.2	-1.2	—
100 mg tid	6.4	-2.0	0.169
200 mg tid	5.9	-3.0	<0.001
*Hours of Wake Time "On"***			
placebo	8.7	1.4	—
100 mg tid	8.1	2.0	0.267
200 mg tid	9.1	2.9	0.008
Secondary Measures			
	Baseline	Change from Baseline at Month 3	p-value*
Levodopa Total Daily Dose (mg)			
placebo	948	16	—
100 mg tid	788	-166	<0.001
200 mg tid	865	-207	<0.001
Global (overall) % Improved			
placebo	—	42	—
100 mg tid	—	71	<0.001
200 mg tid	—	91	<0.001
UPDRS Motor			
placebo	19.5	-0.4	—
100 mg tid	17.6	-1.9	0.217
200 mg tid	20.6	-2.0	0.210
UPDRS ADL			
placebo	7.5	-0.3	—
100 mg tid	7.7	-0.8	0.487
200 mg tid	8.3	0.2	0.412
SIP (total)			
placebo	14.7	-2.2	—
100 mg tid	14.9	-0.4	0.210
200 mg tid	17.6	-0.3	0.216

* Compared to placebo.

** Hours "Off" or "On" are based on the percent of waking day "Off" or "On", assuming a 16-hour waking day.

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Table 2. European Fluctuator Study

Primary Measure			
	Baseline (hrs)	Change from Baseline at Month 3 (hrs)	p-value*
Hours of Wake Time "Off" **			
placebo	6.1	-0.7	—
100 mg tid	6.5	-2.0	0.008
200 mg tid	6.0	-1.6	0.081
Hours of Wake Time "On" **			
placebo	8.5	-0.1	—
100 mg tid	8.1	1.7	0.003
200 mg tid	8.4	1.7	0.003
Secondary Measures			
	Baseline	Change from Baseline at Month 3	p-value*
Levodopa Total Daily Dose (mg)			
placebo	660	-29	—
100 mg tid	667	-109	0.025
200 mg tid	675	-122	0.010
Global (overall) % Improved			
placebo	—	37	—
100 mg tid	—	70	0.003
200 mg tid	—	78	<0.001
UPDRS Motor			
placebo	24.0	-2.1	—
100 mg tid	22.4	-4.2	0.163
200 mg tid	22.4	-6.5	0.004
UPDRS ADL			
placebo	7.9	-0.5	—
100 mg tid	7.5	-0.9	0.408
200 mg tid	7.7	-1.3	0.097
SIP (total)			
placebo	21.6	-0.9	—
100 mg tid	16.6	-1.9	0.419
200 mg tid	18.4	-4.2	0.011

* Compared to placebo.

** Hours "Off" or "On" are based on the percent of waking day "Off" or "On", assuming a 16-hour waking day.

Effects on "Off" time and levodopa dose did not differ by age or sex.

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Non-fluctuating Patients: In this study, 298 patients with idiopathic Parkinson's disease on stable doses of levodopa/carbidopa who were not experiencing wearing-off phenomena were randomized to placebo, tolcapone 100 mg tid, or tolcapone 200 mg tid for 6 months at 20 centers in the United States and Canada. The primary measure of effectiveness was the Activities of Daily Living portion (Subscale II) of the UPDRS. In addition, the change in daily levodopa dose, other subscales of the UPDRS, and the SIP were assessed as secondary measures. The results are displayed in the following table:

Table 3. US/Canadian Non-fluctuator Study

Primary Measure			
	Baseline	Change from Baseline at Month 6	p-value*
UPDRS ADL			
placebo	8.5	0.1	—
100 mg tid	7.5	-1.4	<0.001
200 mg tid	7.9	-1.6	<0.001
Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value*
Levodopa Total Daily Dose (mg)			
placebo	364	47	—
100 mg tid	370	-21	<0.001
200 mg tid	381	-32	<0.001
UPDRS Motor			
placebo	19.7	0.1	—
100 mg tid	17.3	-2.0	0.018
200 mg tid	16.0	-2.3	0.008
SIP (total)			
placebo	6.9	0.4	—
100 mg tid	7.3	-0.9	0.044
200 mg tid	7.3	-0.7	0.078
Percent of Patients who Developed Fluctuations			
placebo	—	26	—
100 mg tid	—	19	0.297
200 mg tid	—	14	0.047

* Compared to placebo.

Effects on Activities of Daily Living did not differ by age or sex.

INDICATIONS: TASMAR is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

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The effectiveness of TASMAR was demonstrated in randomized controlled trials in patients receiving concomitant levodopa therapy with carbidopa or another aromatic amino acid decarboxylase inhibitor who experienced end of dose wearing-off phenomena as well as in patients who did not experience such phenomena (see CLINICAL PHARMACOLOGY: *Clinical Trials*).

CONTRAINDICATIONS: TASMAR tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of TASMAR and a non-selective MAO inhibitor (eg, phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with TASMAR and a non-selective MAO inhibitor.

Tolcapone can be taken concomitantly with a selective MAO-B inhibitor (eg, selegiline).

PRECAUTIONS: ***Hypotension/Syncope:*** Dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension. Tolcapone enhances levodopa bioavailability and, therefore, may increase the occurrence of orthostatic hypotension. In TASMAR clinical trials, orthostatic hypotension was documented at least once in 8%, 14% and 13% of the patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. A total of 2%, 5% and 4% of the patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was invariably not accompanied by vital sign measurements). Patients with orthostasis at baseline were more likely than patients without symptoms to have orthostatic hypotension during the study, irrespective of treatment group. In addition, the effect was greater in tolcapone-treated patients than in placebo-treated patients. Baseline treatment with dopamine agonists or selegiline did not appear to increase the likelihood of experiencing orthostatic hypotension when treated with TASMAR. Approximately 0.7% of the patients treated with TASMAR (5% of patients who were documented to have had at least one episode of orthostatic hypotension) eventually withdrew from treatment due to adverse events presumably related to hypotension.

In controlled Phase 3 trials, approximately 5%, 4% and 3% of tolcapone 200 mg tid, 100 mg tid and placebo patients, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in all three treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement) compared to patients who did not have any episodes of documented hypotension.

Diarrhea: In clinical trials, diarrhea developed in approximately 8%, 16% and 18% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. While diarrhea was generally regarded as mild to moderate in severity, approximately 3% to 4% of patients on

tolcapone had diarrhea which was regarded as severe. Diarrhea was the adverse event which most commonly led to discontinuation, with approximately 1%, 5% and 6% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively, withdrawing from the trials prematurely. Discontinuing TASMAR for diarrhea was related to the severity of the symptom. Diarrhea resulted in withdrawal in approximately 8%, 40% and 70% of patients with mild, moderate and severe diarrhea, respectively. Although diarrhea generally resolved after discontinuation of TASMAR, it led to hospitalization in 0.3%, 0.7% and 1.7% of patients in the placebo, 100 mg and 200 mg TASMAR tid groups.

Typically, diarrhea presents 6 to 12 weeks after tolcapone is started, but it may appear as early as 2 weeks and as late as many months after the initiation of treatment. Clinical trial data suggested that diarrhea associated with tolcapone use may sometimes be associated with anorexia (decreased appetite).

No consistent description of tolcapone-induced diarrhea has been derived from clinical trial data, and the mechanism of action is currently unknown.

It is recommended that all cases of persistent diarrhea should be followed up with an appropriate work-up (including occult blood samples).

Hallucinations: In clinical trials, hallucinations developed in approximately 5%, 8% and 10% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.3%, 1.4% and 1.0% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. Hallucinations led to hospitalization in 0.0%, 1.7% and 0.0% of patients in the placebo, 100 mg and 200 mg TASMAR tid groups, respectively.

In general, hallucinations present shortly after the initiation of therapy with tolcapone (typically within the first 2 weeks). Clinical trial data suggest that hallucinations associated with tolcapone use may be responsive to levodopa dose reduction. Patients whose hallucinations resolved had a mean levodopa dose reduction of 175 mg to 200 mg (20% to 25%) after the onset of the hallucinations. Hallucinations were commonly accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.

Dyskinesia: TASMAR may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 0.0%, 0.3% and 1.0% for placebo, 100 mg and 200 mg TASMAR tid, respectively.

Renal and Hepatic: *Renal Impairment:* No dosage adjustment is needed in patients with mild to moderate renal impairment, however, patients with severe renal impairment should be treated with caution (see CLINICAL PHARMACOLOGY: *Pharmacokinetics of Tolcapone* and DOSAGE AND ADMINISTRATION).

TASMAR® (tolcapone)

Renal Toxicity: When rats were dosed daily for 1 or 2 years (exposures 6 times the human exposure or greater) there was a high incidence of proximal tubule cell damage consisting of degeneration, single cell necrosis, hyperplasia, karyocytomegaly and atypical nuclei. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although it has been speculated that these toxicities may occur as the result of a species-specific mechanism, experiments which would confirm that theory have not been conducted.

Hepatic Impairment: Patients with moderate non-cirrhotic liver disease need no adjustment of dose. Patients with moderate cirrhotic liver disease have reduced clearance of unbound tolcapone by almost 50%, increasing the average concentration of unbound drug by about twofold. Dosage should be reduced in such patients (see CLINICAL PHARMACOLOGY: *Pharmacokinetics of Tolcapone* and DOSAGE AND ADMINISTRATION). Patients with sevère liver impairment should be treated with caution.

Hepatic Enzyme Abnormalities: In Phase 3 controlled trials, increases to more than 3 times the upper limit of normal in ALT or AST occurred in approximately 1% of patients at 100 mg tid and 3% of patients at 200 mg tid. Females were more likely than males to have an increase in hepatic enzymes (approximately 5% vs 2%). Approximately one third of patients with elevated enzymes had diarrhea. Increases to more than 8 times the upper limit of normal in hepatic enzymes occurred in 0.3% at 100 mg tid and 0.7% at 200 mg tid. Elevated enzymes led to discontinuation in 0.3% and 1.7% of patients treated with 100 mg tid and 200 mg tid, respectively. Elevations usually occurred within 6 weeks to 6 months of starting treatment. In about half the cases with elevated hepatic enzymes, enzyme levels returned to baseline values within 1 to 3 months while patients continued TASMAR treatment. When treatment was discontinued, enzymes generally declined within 2 to 3 weeks but in some cases took as long as 1 to 2 months to return to normal.

One patient, a 55-year-old woman who had received treatment with tolcapone 200 mg tid for 53 days, had the onset of diarrhea followed 4 days later by yellowing of the skin and eyes. She died 7 days after the onset of the diarrhea. No liver function tests were performed after the onset of symptoms.

It is recommended that liver enzymes be monitored monthly during the first 3 months of TASMAR treatment, and every 6 weeks for the next 3 months of treatment. Tolcapone should be discontinued for enzyme elevations greater than or equal to 5 times the upper limit of normal or at the appearance of jaundice (see PRECAUTIONS: *Laboratory Tests*).

Hematuria: The rates of hematuria in placebo-controlled trials were approximately 2%, 4% and 5% in placebo, 100 mg and 200 mg TASMAR tid, respectively. The etiology of the increase with TASMAR has not always been explained (for example, by urinary tract infection or coumadin therapy). In placebo-controlled trials in the United States (N=593) rates of microscopically confirmed hematuria were approximately 3%, 2% and 2% in placebo, 100 mg and 200 mg TASMAR tid, respectively.

TASMAR® (tolcapone)

Events Reported With Dopaminergic Therapy: The events listed below are known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists. While cases of Withdrawal Emergent Hyperpyrexia and Confusion have been reported in association with tolcapone withdrawal (see below), the expected incidence of fibrotic complications is so low that even if tolcapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that even a single example would have been detected in a cohort of the size exposed to tolcapone.

Withdrawal Emergent Hyperpyrexia and Confusion: Four cases of a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, and altered consciousness), similar to that reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs, have been reported in association with the abrupt withdrawal or lowering of the dose of tolcapone. In 3 of these cases, CPK was elevated as well. One patient died, and the other 3 patients recovered over periods of approximately 2, 4 and 6 weeks.

Fibrotic Complications: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (eg, tolcapone) that increase dopaminergic activity can cause them is unknown.

Three cases of pleural effusion, one with pulmonary fibrosis, occurred during clinical trials. These patients were also on concomitant dopamine agonists (pergolide or bromocriptine) and had a prior history of cardiac disease or pulmonary pathology (nonmalignant lung lesion).

Information for Patients: Patients should be instructed to take TASMAR only as prescribed.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with TASMAR.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on TASMAR to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with TASMAR.

Patients should be informed that nausea may occur, especially at the initiation of treatment with TASMAR.

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Patients should be advised of the possibility of an increase in dyskinesia and/or dystonia.

Although TASMAR has not been shown to be teratogenic in animals, it is always given in conjunction with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS: *Pregnancy*).

Tolcapone is excreted into maternal milk in rats. Because of the possibility that tolcapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Laboratory Tests: It is recommended that transaminases be monitored monthly for the first 3 months of treatment with TASMAR, after which LFTs should be monitored every 6 weeks for the next 3 months. If elevations occur, and a decision is made to continue to treat the patient, more frequent monitoring of complete liver function is recommended. Treatment should be discontinued if ALT exceeds 5 x ULN or if jaundice develops.

Special Populations: Parkinson's disease patients with moderate to severe liver impairment or severe renal impairment should be treated with caution (see DOSAGE AND ADMINISTRATION).

Drug Interactions: *Protein Binding:* Although tolcapone is highly protein bound, in vitro studies have shown that tolcapone at a concentration of 50 μg/mL did not displace other highly protein-bound drugs from their binding sites at therapeutic concentrations. The experiments included warfarin (0.5 to 7.2 μg/mL), phenytoin (4.0 to 38.7 μg/mL), tolbutamide (24.5 to 96.1 μg/mL) and digitoxin (9.0 to 27.0 μg/mL).

Drugs Metabolized by Catechol-O-methyltransferase (COMT): Tolcapone may influence the pharmacokinetics of drugs metabolized by COMT. However, no effects were seen on the pharmacokinetics of the COMT substrate carbidopa. The effect of tolcapone on the pharmacokinetics of other drugs of this class such as α-methyldopa, dobutamine, apomorphine, and isoproterenol has not been evaluated. A dose reduction of such compounds should be considered when they are coadministered with tolcapone.

Effect of Tolcapone on the Metabolism of Other Drugs: In vitro experiments have been performed to assess the potential of tolcapone to interact with isoenzymes of cytochrome P450 (CYP). No relevant interactions with substrates for CYP 2A6 (coumadin), CYP 1A2 (caffeine), CYP 3A4 (midazolam, terfenadine, cyclosporine), CYP 2C19 (S-mephenytoin) and CYP 2D6 (desipramine) were observed in vitro. The absence of an interaction with desipramine, a drug metabolized by cytochrome P450 2D6, was also confirmed in an in vivo study where tolcapone did not change the pharmacokinetics of desipramine.

Due to its affinity to cytochrome P450 2C9 in vitro, tolcapone may interfere with drugs, whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. However, in an in vivo interaction study, tolcapone did not change the pharmacokinetics of tolbutamide.

Therefore, clinically relevant interactions involving cytochrome P450 2C9 appear unlikely. Similarly, tolcapone did not affect the pharmacokinetics of desipramine, a drug metabolized by cytochrome P450 2D6, indicating that interactions with drugs metabolized by that enzyme are unlikely. Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these two drugs are coadministered.

Drugs That Increase Catecholamines: Tolcapone did not influence the effect of ephedrine, an indirect sympathomimetic, on hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise. Since tolcapone did not alter the tolerability of ephedrine, these drugs can be coadministered.

When TASMAR was given together with levodopa/carbidopa and desipramine, there was no significant change in blood pressure, pulse rate and plasma concentrations of desipramine. Overall, the frequency of adverse events increased slightly. These adverse events were predictable based on the known adverse reactions to each of the three drugs individually. Therefore, caution should be exercised when desipramine is administered to Parkinson's disease patients being treated with TASMAR and levodopa/carbidopa.

In clinical trials, patients receiving TASMAR/levodopa preparations reported a similar adverse event profile independent of whether or not they were also concomitantly administered selegiline (a selective MAO-B inhibitor).

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* Carcinogenicity studies in which tolcapone was administered in the diet were conducted in mice and rats. Mice were treated for 80 (female) or 95 (male) weeks with doses of 100, 300 and 800 mg/kg/day, equivalent to 0.8, 1.6 and 4 times human exposure (AUC = 80 ug·hr/mL) at the recommended daily clinical dose of 600 mg. Rats were treated for 104 weeks with doses of 50, 250 and 450 mg/kg/day. Tolcapone exposures were 1, 6.3 and 13 times the human exposure in male rats and 1.7, 11.8 and 26.4 times the human exposure in female rats. There was an increased incidence of uterine adenocarcinomas in female rats at exposure equivalent to 26.4 times the human exposure. There was evidence of renal tubular injury and renal tubular tumor formation in rats. A low incidence of renal tubular cell adenomas occurred in middle- and high-dose female rats; tubular cell carcinomas occurred in middle- and high-dose male and high-dose female rats, with a statistically significant increase in high-dose males. Exposures were equivalent to 6.3 (males) or 11.8 (females) times the human exposure or greater; no renal tumors were observed at exposures of 1 (males) or 1.7 (females) times the human exposure. Minimal-to-marked damage to the renal tubules, consisting of proximal tubule cell degeneration, singe cell necrosis, hyperplasia and karyocytomegaly, occurred at the doses associated with renal tumors. Renal tubule damage, characterized by proximal tubule cell degeneration and the presence of atypical nuclei, as well as one adenocarcinoma in a high-dose male, were observed in a 1-year study in rats receiving doses of tolcapone of 150 and 450 mg/kg/day. These histopathological changes suggest the possibility that renal tumor formation might be secondary to chronic cell damage and sustained repair, but this relationship has not been established, and the relevance of these findings to humans is not known. There was no evidence of carcinogenic effects in the long-term mouse study. The

carcinogenic potential of tolcapone in combination with levodopa/carbidopa has not been examined.

Mutagenesis: Tolcapone was clastogenic in the in vitro mouse lymphoma/thymidine kinase assay in the presence of metabolic activation. Tolcapone was not mutagenic in the Ames test, the in vitro V79/HPRT gene mutation assay, or the unscheduled DNA synthesis assay. It was not clastogenic in an in vitro chromosomal aberration assay in cultured human lymphocytes, or an in vivo micronucleus assay in mice.

Impairment of Fertility: Tolcapone did not affect fertility and general reproductive performance in rats at doses up to 300 mg/kg/day (5.7 times the human dose on a mg/m^2 basis).

Pregnancy: Pregnancy Category C. Tolcapone, when administered alone during organogenesis, was not teratogenic at doses of up to 300 mg/kg/day in rats or up to 400 mg/kg/day in rabbits (5.7 times and 15 times the recommended daily clinical dose of 600 mg, on a mg/m^2 basis, respectively). In rabbits, however, an increased rate of abortion occurred at a dose of 100 mg/kg/day (3.7 times the daily clinical dose on a mg/m^2 basis) or greater. Evidence of maternal toxicity (decreased weight gain, death) was observed at 300 mg/kg in rats and 400 mg/kg in rabbits. When tolcapone was administered to female rats during the last part of gestation and throughout lactation, decreased litter size and impaired growth and learning performance in female pups were observed at a dose of 250/150 mg/kg/day (dose reduced from 250 to 150 mg/kg/day during late gestation due to high rate of maternal mortality; equivalent to 4.8/2.9 times the clinical dose on a mg/m^2 basis).

Tolcapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa (80/20 mg/kg/day) produced an increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis. Plasma exposures to tolcapone (based on AUC) were 0.5 times the expected human exposure, and plasma exposures to levodopa were 6 times higher than those in humans under therapeutic conditions. In a combination embryo-fetal development study in rats, fetal body weights were reduced by the combination of tolcapone (10, 30 and 50 mg/kg/day) and levodopa/carbidopa (120/30 mg/kg/day) and by levodopa/carbidopa alone. Tolcapone exposures were 0.5 times expected human exposure or greater: levodopa exposures were 21 times expected human exposure or greater. The high dose of 50 mg/kg/day of tolcapone given alone was not associated with reduced fetal body weight (plasma exposures of 1.4 times the expected human exposure).

There is no experience from clinical studies regarding the use of TASMAR in pregnant women. Therefore, TASMAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: In animal studies, tolcapone was excreted into maternal rat milk.

It is not known whether tolcapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tolcapone is administered to a nursing woman.

TASMAR® (tolcapone)

Pediatric Use: There is no identified potential use of tolcapone in pediatric patients.

ADVERSE REACTIONS: During the pre-marketing development of tolcapone, two distinct patient populations were studied, patients with end-of-dose wearing-off phenomena and patients with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects. Adverse events are, therefore, shown for these two populations combined.

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials (N=892) associated with the use of TASMAR not seen at an equivalent frequency among the placebo-treated patients were dyskinesia, nausea, sleep disorder, dystonia, dreaming excessive, anorexia, cramps muscle, orthostatic complaints, somnolence, diarrhea, confusion, dizziness, headache, hallucination, vomiting, constipation, fatigue, upper respiratory tract infection, falling, sweating increased, urinary tract infection, xerostomia, abdominal pain, urine discoloration.

Approximately 16% of the 592 patients who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared to 10% of the 298 patients who received placebo. Diarrhea was by far the most frequent cause of discontinuation (approximately 6% in tolcapone patients vs 1% on placebo).

Adverse Event Incidence in Controlled Clinical Studies: Table 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with tolcapone participating in the double-blind, placebo-controlled studies and were numerically more common in at least one of the tolcapone groups. In these studies, either tolcapone or placebo were added to levodopa/carbidopa (or benserazide).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events incidence rate in the population studied.

TASMAR® (tolcapone)

Table 4. Summary of Patients With Adverse Events After Start of Trial Drug Administration
(At Least 1% in TASMAR Group and at Least One TASMAR Dose Group > Placebo)

	Placebo	Tolcapone tid	
		100 mg	200 mg
	N = 298	N = 296	N = 298
Adverse Events	(%)	(%)	(%)
Dyskinesia	20	42	51
Nausea	18	30	35
Sleep Disorder	18	24	25
Dystonia	17	19	22
Dreaming Excessive	17	21	16
Anorexia	13	19	23
Cramps Muscle	17	17	18
Orthostatic Complaints	14	17	17
Somnolence	13	18	14
Diarrhea	8	16	18
Confusion	9	11	10
Dizziness	10	13	6
Headache	7	10	11
Hallucination	5	8	10
Vomiting	4	8	10
Constipation	5	6	8
Fatigue	6	7	3
Upper Respiratory Tract Infection	3	5	7
Falling	4	4	6
Sweating Increased	2	4	7
Urinary Tract Infection	4	5	5
Xerostomia	2	5	6
Abdominal Pain	3	5	6
Syncope	3	4	5
Urine Discoloration	1	2	7
Dyspepsia	2	4	3
Influenza	2	3	4
Dyspnea	2	3	3
Balance Loss	2	3	2
Flatulence	2	2	4
Hyperkinesia	1	3	2
Chest Pain	1	3	1
Hypotension	1	2	2
Paresthesia	2	3	1
Stiffness	1	2	2
Arthritis	1	2	1

TASMAR® (tolcapone)

	Placebo	Tolcapone tid	
		100 mg	200 mg
	N = 298	N = 296	N = 298
Adverse Events	(%)	(%)	(%)
Chest Discomfort	1	1	2
Hypokinesia	1	1	3
Micturition Disorder	1	2	1
Pain Neck	1	2	2
Burning	0	2	1
Sinus Congestion	0	2	1
Agitation	0	1	1
Bleeding Dermal	0	1	1
Irritability	0	1	1
Mental Deficiency	0	1	1
Hyperactivity	0	1	1
Malaise	0	1	0
Panic Reaction	0	1	0
Tumor Skin	0	1	0
Cataract	0	1	0
Euphoria	0	1	0
Fever	0	0	1
Alopecia	0	1	0
Eye Inflamed	0	1	0
Hypertonia	0	0	1
Tumor Uterus	0	1	0

Other events reported by 1% or more of patients treated with TASMAR but that were equally or more frequent in the placebo group were arthralgia, pain limbs, anxiety, micturition frequency, fractures, vision blurred, pneumonia, paresis, lethargy, asthenia, edema peripheral, gait abnormal, taste alteration, weight decrease and sinusitis.

Effects of Gender and Age on Adverse Reactions: Experience in clinical trials have suggested that patients greater than 75 years of age may be more likely to develop hallucinations than patients less than 75 years of age, while patients over 75 may be less likely to develop dystonia. Females may be more likely to develop somnolence than males.

Other Adverse Events Observed During All Trials in Patients With Parkinson's Disease: TASMAR has been administered in 1536 patients with Parkinson's disease in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of adverse events were grouped into a smaller number of standardized categories using COSTART dictionary terminology. These categories are used in the listing below.

TASMAR® (tolcapone)

All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events and terms too vague to be meaningful are included, without regard to determination of a causal relationship to TASMAR.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are defined as those occurring in between 1/100 and 1/1000 patients; and rare adverse events are defined as those occurring in fewer than 1/1000 patients.

Nervous System — frequent: depression, hypesthesia, tremor, speech disorder, vertigo, emotional lability; *infrequent:* neuralgia, amnesia, extrapyramidal syndrome, hostility, libido increased, manic reaction, nervousness, paranoid reaction, cerebral ischemia, cerebrovascular accident, delusions, libido decreased, neuropathy, apathy, choreoathetosis, myoclonus, psychosis, thinking abnormal, twitching; *rare:* antisocial reaction, delirium, encephalopathy, hemiplegia, meningitis.

Digestive System — frequent: tooth disorder; *infrequent:* dysphagia, gastrointestinal hemorrhage, gastroenteritis, mouth ulceration, increased salivation, abnormal stools, esophagitis, cholelithiasis, colitis, tongue disorder, rectal disorder; *rare:* cholecystitis, duodenal ulcer, gastrointestinal carcinoma, stomach atony.

Body as a Whole — frequent: flank pain, accidental injury, abdominal pain, infection; *infrequent:* hernia, pain, allergic reaction, cellulitis, infection fungal, viral infection, carcinoma, chills, infection bacterial, neoplasm, abscess, face edema; *rare:* death.

Cardiovascular System — frequent: palpitation; *infrequent:* hypertension, vasodilation, angina pectoris, heart failure, atrial fibrillation, tachycardia, migraine, aortic stenosis, arrythmia, arteriospasm, bradycardia, cerebral hemorrhage, coronary artery disorder, heart arrest, myocardial infarct, myocardial ischemia, pulmonary embolus; *rare:* arteriosclerosis, cardiovascular disorder, pericardial effusion, thrombosis.

Musculoskeletal System — frequent: myalgia; *infrequent:* tenosynovitis, arthrosis, joint disorder.

Urogenital System — frequent: urinary incontinence, impotence; *infrequent:* prostatic disorder, dysuria, nocturia, polyuria, urinary retention, urinary tract disorder, hematuria, kidney calculus, prostatic carcinoma, breast neoplasm, oliguria, uterine atony, uterine disorder, vaginitis; *rare:* bladder calculus, ovarian carcinoma, uterine hemorrhage.

Respiratory System — frequent: bronchitis, pharyngitis; *infrequent:* cough increased, rhinitis, asthma, epistaxis, hyperventilation, laryngitis, hiccup; *rare:* apnea, hypoxia, lung edema.

Skin and Appendages — frequent: rash; *infrequent:* herpes zoster, pruritus, seborrhea, skin discoloration, eczema, erythema multiforme, skin disorder, furunculosis, herpes simplex, urticaria.

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Special Senses — frequent: tinnitus; *infrequent:* diplopia, ear pain, eye hemorrhage, eye pain, lacrimation disorder, otitis media, parosmia; *rare:* glaucoma.

Metabolic and Nutritional — infrequent: edema, hypercholesteremia, thirst, dehydration.

Hemic and Lymphatic System — infrequent: anemia; *rare:* leukemia, thrombocytopenia.

Endocrine System — infrequent: diabetes mellitus.

Unclassified — infrequent: surgical procedure.

DRUG ABUSE AND DEPENDENCE: Tolcapone is not a controlled substance.

Studies conducted in rats and monkeys did not reveal any potential for physical or psychological dependence. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

OVERDOSAGE: The highest dose of tolcapone administered to humans was 800 mg tid, with and without levodopa/carbidopa coadministration. This was in a 1-week study in elderly, healthy volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 μg/mL (compared to 3 μg/mL and 6 μg/mL with 100 mg and 200 mg tolcapone, respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa/carbidopa.

The threshold for the lethal plasma concentration for tolcapone based on animal data is >100 μg/mL. Respiratory difficulties were observed in rats at high oral (gavage) and intravenous doses and in dogs with rapidly injected intravenous doses.

Management of Overdose: Hospitalization is advised. General supportive care is indicated. Based on the physicochemical properties of the compound, hemodialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: Therapy with TASMAR may be initiated with 100 mg or 200 mg tid, always as an adjunct to levodopa/carbidopa therapy. Although clinical trial data suggest that initial treatment with 200 mg tid (a daily dose of 600 mg) is reasonably well tolerated, the prescriber may wish to begin treatment with 100 mg tid because of the potential for increased dopaminergic side effects (eg, dyskinesias) and the possible necessary adjustment of the concomitant levodopa/carbidopa dose. In clinical trials, the first dose of the day of TASMAR was always taken together with the first dose of the day of levodopa/carbidopa, and the subsequent doses of TASMAR were given approximately 6 and 12 hours later.

In clinical trials, the majority of patients required a decrease in their daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias before beginning treatment.

TASMAR® (tolcapone)

The maximum recommended dose of TASMAR is 600 mg a day, given as tid dosing. To optimize an individual patient's response, reductions in daily levodopa dose may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 30% in those patients requiring a levodopa dose reduction. (Greater than 70% of patients with levodopa doses above 600 mg daily required such a reduction.)

The safety and effectiveness of daily doses greater than 600 mg, or of single doses greater than 200 mg, have not been systematically evaluated.

TASMAR can be combined with both the immediate and sustained release formulations of levodopa/carbidopa.

TASMAR may be taken with or without food (see CLINICAL PHARMACOLOGY).

Patients With Impaired Renal or Hepatic Function: Patients with moderate to severe cirrhosis of the liver should not be escalated to 200 mg TASMAR tid (see CLINICAL PHARMACOLOGY).

No dose adjustment of TASMAR is recommended for patients with mild to moderate renal impairment. The safety of tolcapone has not been examined in subjects who had creatinine clearance less than 25 mL/min (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED: TASMAR is supplied as film-coated tablets containing 100 mg or 200 mg tolcapone. The 100 mg beige tablet and the 200 mg reddish-brown tablet are hexagonal and biconvex. Imprinted with black ink on one side of the tablet is TASMAR and the tablet strength (100 or 200), on the other side is ROCHE.

TASMAR 100 mg Tablets: bottles of 90 (NDC 0004-5920-01).

TASMAR 200 mg Tablets: bottles of 90 (NDC 0004-5921-01).

Storage: Store at controlled room temperature 20° to 25°C (68° to 77°F) in tight containers as defined in USP/NF.

TASMAR® (tolcapone)

(Roche Hexagon)

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

25703287-0198

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(2)

FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859
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DATE:	**January 29, 1998**
TIME:	**4:15pm**
DELIVER TO:	**Tom Watson**
Fax Number:	973-562-3700
Phone Number:	973-562-3724

FROM:	**Jackie Ware, Pharm.D.** 301-594-5793 Project Manager

Total number of pages, including cover page: 25 (1 cover page, 2 page letter, 22 pages of labeling)

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:
Tom,

Following is a copy of the approval letter for NDA 20-697 (Tasmar Tablets). The official copy will be sent to you via mail.

Congratulations,
Jackie

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-697

JAN 29 1998

Hoffman-La Roche Inc.
Attention: Thomas Watson
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Mr. Watson:

Please refer to your new drug application dated June 03, 1996, and your resubmission dated July 28, 1997 and received July 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tasmar (tolcapone) 100 mg & 200 mg tablets.

We acknowledge receipt of your submissions dated:

July 30, 1997	September 2, 1997	September 12, 1997
October 21, 1997	December 5, 1997	

The User Fee goal date for this application is January 30, 1998.

This new drug application provides for the following indication:

> Tasmar™ is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.
>
> The effectiveness of Tasmar™ was demonstrated in randomized controlled trials in patients receiving concomitant levodopa therapy with carbidopa or another aromatic amino acid decarboxylase inhibitor who experienced end of dose wearing-off phenomena as well as in patients who did not experience such phenomena.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or

similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-697. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

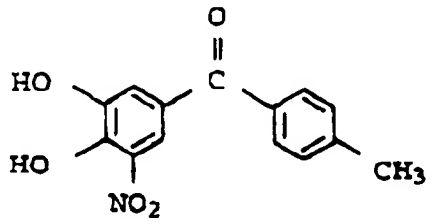
Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

(Roche Hexagon)

TASMAR®
(tolcapone)
TABLETS

DESCRIPTION: TASMAR® is available as tablets containing 100 mg or 200 mg tolcapone.

Tolcapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. It is a yellow, odorless, non-hygroscopic, crystalline compound with a relative molecular mass of 273.25. The chemical name of tolcapone is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone. Its empirical formula is $C_{14}H_{11}NO_5$ and its structural formula is:



Inactive ingredients: Core: lactose monohydrate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc and magnesium stearate. Film coating: hydroxypropyl methyl cellulose, titanium dioxide, talc, ethylcellulose, triacetin and sodium lauryl sulfate, with the following dye systems: 100 mg—yellow and red iron oxide; 200 mg—red iron oxide.

CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** Tolcapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs. The highest activities are in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

TASMAR® (tolcapone)

The precise mechanism of action of tolcapone is unknown, but it is believed to be related to its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When tolcapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that these sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease in patients as well as increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa. Tolcapone enters the CNS to a minimal extent, but has been shown to inhibit central COMT activity in animals.

Pharmacodynamics: *COMT Activity in Erythrocytes:* Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. The inhibition is closely related to plasma tolcapone concentrations. With a 200 mg single dose of tolcapone, maximum inhibition of erythrocyte COMT activity is on average greater than 80%. During multiple dosing with tolcapone (200 mg tid), erythrocyte COMT inhibition at trough tolcapone blood concentrations is 30% to 45%.

Effect on the Pharmacokinetics of Levodopa and its Metabolites: When tolcapone is administered together with levodopa/carbidopa, it increases the relative bioavailability (AUC) of levodopa by approximately twofold. This is due to a decrease in levodopa clearance resulting in a prolongation of the terminal elimination half-life of levodopa (from approximately 2 hours to 3.5 hours). In general, the average peak levodopa plasma concentration (C_{max}) and the time of its occurrence (T_{max}) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment. Studies in healthy volunteers and Parkinson's disease patients have confirmed that the maximal effect occurs with 100 mg to 200 mg tolcapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by tolcapone when given with levodopa/carbidopa.

Population pharmacokinetic analyses in patients with Parkinson's disease have shown the same effects of tolcapone on levodopa plasma concentrations that occur in healthy volunteers.

Pharmacokinetics of Tolcapone: Tolcapone pharmacokinetics are linear over the dose range of 50 mg to 400 mg, independent of levodopa/carbidopa coadministration. The elimination half-life of tolcapone is 2 to 3 hours and there is no significant accumulation. With tid dosing of 100 mg or 200 mg, C_{max} is approximately 3 μg/mL and 6 μg/mL, respectively.

Absorption: Tolcapone is rapidly absorbed, with a T_{max} of approximately 2 hours. The absolute bioavailability following oral administration is about 65%. Food given within 1 hour before and 2 hours after dosing of tolcapone decreases the relative bioavailability by 10% to 20% (see DOSAGE AND ADMINISTRATION).

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Distribution: The steady-state volume of distribution of tolcapone is small (9 L). Tolcapone does not distribute widely into tissues due to its high plasma protein binding. The plasma protein binding of tolcapone is >99.9% over the concentration range of 0.32 to 210 μg/mL. In vitro experiments have shown that tolcapone binds mainly to serum albumin.

Metabolism and Elimination: Tolcapone is almost completely metabolized prior to excretion, with only a very small amount (0.5% of dose) found unchanged in urine. The main metabolic pathway of tolcapone is glucuronidation; the glucuronide conjugate is inactive. In addition, the compound is methylated by COMT to 3-O-methyl-tolcapone. Tolcapone is metabolized to a primary alcohol (hydroxylation of the methyl group), which is subsequently oxidized to the carboxylic acid. In vitro experiments suggest that the oxidation may be catalyzed by cytochrome P450 3A4 and P450 2A6. The reduction to an amine and subsequent N-acetylation occur to a minor extent. After oral administration of a ^{14}C-labeled dose of tolcapone, 60% of labeled material is excreted in urine and 40% in feces.

Tolcapone is a low-extraction ratio drug (extraction ratio = 0.15) with a moderate systemic clearance of about 7L/h.

Special Populations: Tolcapone pharmacokinetics are independent of sex, age, body weight, and race (Japanese, Black and Caucasian). Polymorphic metabolism is unlikely based on the metabolic pathways involved.

Hepatic Impairment: A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. In patients with moderate cirrhotic liver disease (Child-Pugh Class B), however, clearance and volume of distribution of unbound tolcapone was reduced by almost 50%. This reduction may increase the average concentration of unbound drug by twofold (see DOSAGE AND ADMINISTRATION).

Renal Impairment: The pharmacokinetics of tolcapone have not been investigated in a specific renal impairment study. However, the relationship of renal function and tolcapone pharmacokinetics has been investigated using population pharmacokinetics during clinical trials. The data of more than 400 patients have confirmed that over a wide range of creatinine clearance values (30 mL/min to 130 mL/min) the pharmacokinetics of tolcapone are unaffected by renal function. This could be explained by the fact that only a negligible amount of unchanged tolcapone (0.5%) is excreted in the urine. The glucuronide conjugate of tolcapone is mainly excreted in the urine but is also excreted in the bile. Accumulation of this stable and inactive metabolite should not present a risk in renally impaired patients with creatinine clearance above 25 mL/min (see DOSAGE AND ADMINISTRATION). Given the very high protein binding of tolcapone, no significant removal of the drug by hemodialysis would be expected.

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Drug Interactions: See PRECAUTIONS: *Drug Interactions*.

Clinical Studies: The effectiveness of TASMAR as an adjunct to levodopa in the treatment of Parkinson's disease was established in 3 multicenter randomized controlled trials of 13 to 26 weeks duration, supported by four 6-week trials whose results were consistent with those of the longer trials. In two of the longer trials, tolcapone was evaluated in patients whose Parkinson's disease was characterized by deterioration in their response to levodopa at the end of a dosing interval (so-called fluctuating patients with wearing-off phenomena). In the remaining trial, tolcapone was evaluated in patients whose response to levodopa was relatively stable (so-called non-fluctuators).

Fluctuating Patients: In two 3-month trials, patients with documented episodes of wearing-off phenomena, despite optimum levodopa therapy, were randomized to receive placebo, tolcapone 100 mg tid or 200 mg tid. The formal double-blind portion of the trial was 3 months long, and the primary outcome was a comparison between treatments in the change from baseline in the amount of time spent "On" (a period of relatively good functioning) and "Off" (a period of relatively poor functioning). Patients recorded periodically, throughout the duration of the trial, the time spent in each of these states.

In addition to the primary outcome, patients were also assessed using sub-parts of the Unified Parkinson's Disease Rating Scale (UPDRS), a frequently used multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor function (Part III), complications of therapy (Part IV), and disease staging (Part V & VI); an Investigator's Global Assessment of Change (IGA), a subjective scale designed to assess global functioning in 5 areas of Parkinson's disease; the Sickness Impact Profile (SIP), a multi-item scale in 12 domains designed to assess the patient's functioning in multiple areas; and the change in daily Sinemet dose.

In one of the studies, 202 patients were randomized in 11 centers in the United States and Canada. In this trial, all patients were receiving concomitant levodopa and carbidopa. In the second trial, 177 patients were randomized in 24 centers in Europe. In this trial, all patients were receiving concomitant levodopa and benserazide.

The following tables display the results of these 2 trials:

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Table 1. US/Canadian Fluctuator Study

	Baseline (hrs)	Change from Baseline at Month 3 (hrs)	p-value*
Primary Measure			
*Hours of Wake Time "Off"***			
placebo	6.2	-1.2	—
100 mg tid	6.4	-2.0	0.169
200 mg tid	5.9	-3.0	0.001
*Hours of Wake Time "On"***			
placebo	8.7	1.4	—
100 mg tid	8.1	2.0	0.267
200 mg tid	9.1	2.9	0.008
Secondary Measures			
	Baseline	Change from Baseline at Month 3	p-value*
Levodopa Total Daily Dose (mg)			
placebo	948	16	—
100 mg tid	788	-166	<0.001
200 mg tid	865	-207	<0.001
Global (overall) % Improved			
placebo	—	42	—
100 mg tid	—	71	<0.001
200 mg tid	—	91	<0.001
UPDRS Motor			
placebo	19.5	-0.4	—
100 mg tid	17.6	-1.9	0.217
200 mg tid	20.6	-2.0	0.210
UPDRS ADL			
placebo	7.5	-0.3	—
100 mg tid	7.7	-0.8	0.487
200 mg tid	8.3	0.2	0.412
SIP (total)			
placebo	14.7	-2.2	—
100 mg tid	14.9	-0.4	0.210
200 mg tid	17.6	-0.3	0.216

* Compared to placebo. ** Hours "Off" or "On" are based on the percent of waking day "Off" or "On" assuming a 16-hour waking day.

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Table 2. European Fluctuator Study

	Baseline (hrs)	Change from Baseline at Month 3 (hrs)	p-value*
Primary Measure			
Hours of Wake Time "Off" **			
placebo	6.1	-0.7	—
100 mg tid	6.5	-2.0	0.008
200 mg tid	6.0	-1.6	0.081
Hours of Wake Time "On" **			
placebo	8.5	-0.1	—
100 mg tid	8.1	1.7	0.003
200 mg tid	8.4	1.7	0.003
Secondary Measures			
	Baseline	Change from Baseline at Month 3	p-value*
Levodopa Total Daily Dose (mg)			
placebo	660	-29	—
100 mg tid	667	-109	0.025
200 mg tid	675	-122	0.010
Global (overall) % Improved			
placebo	—	37	—
100 mg tid	—	70	0.003
200 mg tid	—	78	<0.001
UPDRS Motor			
placebo	24.0	-2.1	—
100 mg tid	22.4	-4.2	0.163
200 mg tid	22.4	-6.5	0.004
UPDRS ADL			
placebo	7.9	-0.5	—
100 mg tid	7.5	-0.9	0.408
200 mg tid	7.7	-1.3	0.097
SIP (total)			
placebo	21.6	-0.9	—
100 mg tid	16.6	-1.9	0.419
200 mg tid	18.4	-4.2	0.011

* Compared to placebo. ** Hours "Off" or "On" are based on the percent of waking day "Off" or "On" assuming a 16-hour waking day.

Effects on "Off" time and levodopa dose did not differ by age or sex.

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Non-fluctuating Patients: In this study, 298 patients with idiopathic Parkinson's disease on stable doses of levodopa/carbidopa who were not experiencing wearing-off phenomena were randomized to placebo, tolcapone 100 mg tid, or tolcapone 200 mg tid for 6 months at 20 centers in the United States and Canada. The primary measure of effectiveness was the Activities of Daily Living portion (Subscale II) of the UPDRS. In addition, the change in daily levodopa dose, other subscales of the UPDRS, and the SIP were assessed as secondary measures. The results are displayed in the following table:

Table 3. US/Canadian Non-fluctuator Study

Primary Measure			
	Baseline	Change from Baseline at Month 6	p-value*
UPDRS ADL			
placebo	8.5	0.1	—
100 mg tid	7.5	-1.4	<0.001
200 mg tid	7.9	-1.6	<0.001
Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value*
Levodopa Total Daily Dose (mg)			
placebo	364	47	—
100 mg tid	370	-21	<0.001
200 mg tid	381	-32	<0.001
UPDRS Motor			
placebo	19.7	0.1	—
100 mg tid	17.3	-2.0	0.018
200 mg tid	16.0	-2.3	0.008
SIP (total)			
placebo	6.9	0.4	—
100 mg tid	7.3	-0.9	0.044
200 mg tid	7.3	-0.7	0.078
Percent of Patients who Developed Fluctuations			
placebo	—	26	—
100 mg tid	—	19	0.297
200 mg tid	—	14	0.047

* Compared to placebo.

Effects on Activities of Daily Living did not differ by age or sex.

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INDICATIONS: TASMAR is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of TASMAR was demonstrated in randomized controlled trials in patients receiving concomitant levodopa therapy with carbidopa or another aromatic amino acid decarboxylase inhibitor who experienced end of dose wearing-off phenomena as well as in patients who did not experience such phenomena (see CLINICAL PHARMACOLOGY: *Clinical Trials*).

CONTRAINDICATIONS: TASMAR tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of TASMAR and a non-selective MAO inhibitor (eg, phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with TASMAR and a non-selective MAO inhibitor.

Tolcapone can be taken concomitantly with a selective MAO-B inhibitor (eg, selegiline).

PRECAUTIONS: ***Hypotension/Syncope:*** Dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension. Tolcapone enhances levodopa bioavailability and, therefore, may increase the occurrence of orthostatic hypotension. In TASMAR clinical trials, orthostatic hypotension was documented at least once in 8%, 14% and 13% of the patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. A total of 2%, 5% and 4% of the patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was invariably not accompanied by vital sign measurements). Patients with orthostasis at baseline were more likely than patients without symptoms to have orthostatic hypotension during the study, irrespective of treatment group. In addition, the effect was greater in tolcapone-treated patients than in placebo-treated patients. Baseline treatment with dopamine agonists or selegiline did not appear to increase the likelihood of experiencing orthostatic hypotension when treated with TASMAR. Approximately 0.7% of the patients treated with TASMAR (5% of patients who were documented to have had at least one episode of orthostatic hypotension) eventually withdrew from treatment due to adverse events presumably related to hypotension.

In controlled Phase 3 trials, approximately 5%, 4% and 3% of tolcapone 200 mg tid, 100 mg tid and placebo patients, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in all three treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement) compared to patients who did not have any episodes of documented hypotension.

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Diarrhea: In clinical trials, diarrhea developed in approximately 8%, 16% and 18% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. While diarrhea was generally regarded as mild to moderate in severity, approximately 3% to 4% of patients on tolcapone had diarrhea which was regarded as severe. Diarrhea was the adverse event which most commonly led to discontinuation, with approximately 1%, 5% and 6% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively, withdrawing from the trials prematurely. Discontinuing TASMAR for diarrhea was related to the severity of the symptom. Diarrhea resulted in withdrawal in approximately 8%, 40% and 70% of patients with mild, moderate and severe diarrhea, respectively. Although diarrhea generally resolved after discontinuation of TASMAR, it led to hospitalization in 0.3%, 0.7% and 1.7% of patients in the placebo, 100 mg and 200 mg TASMAR tid groups.

Typically, diarrhea presents 6 to 12 weeks after tolcapone is started, but it may appear as early as 2 weeks and as late as many months after the initiation of treatment. Clinical trial data suggested that diarrhea associated with tolcapone use may sometimes be associated with anorexia (decreased appetite).

No consistent description of tolcapone-induced diarrhea has been derived from clinical trial data, and the mechanism of action is currently unknown.

It is recommended that all cases of persistent diarrhea should be followed up with an appropriate work-up (including occult blood samples).

Hallucinations: In clinical trials, hallucinations developed in approximately 5%, 8% and 10% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.3%, 1.4% and 1.0% of patients treated with placebo, 100 mg and 200 mg TASMAR tid, respectively. Hallucinations led to hospitalization in 0.0%, 1.7% and 0.0% of patients in the placebo, 100 mg and 200 mg TASMAR tid groups, respectively.

In general, hallucinations present shortly after the initiation of therapy with tolcapone (typically within the first 2 weeks). Clinical trial data suggest that hallucinations associated with tolcapone use may be responsive to levodopa dose reduction. Patients whose hallucinations resolved had a mean levodopa dose reduction of 175 mg to 200 mg (20% to 25%) after the onset of the hallucinations. Hallucinations were commonly accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.

Dyskinesia: TASMAR may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 0.0%, 0.3% and 1.0% for placebo, 100 mg and 200 mg tid.

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Renal and Hepatic: *Renal Impairment:* No dosage adjustment is needed in patients with mild to moderate renal impairment, however, patients with severe renal impairment should be treated with caution (see CLINICAL PHARMACOLOGY: *Pharmacokinetics of Tolcapone* and DOSAGE AND ADMINISTRATION).

Renal Toxicity: When rats were dosed daily for 1 or 2 years (exposures 6 times the human exposure or greater) there was a high incidence of proximal tubule cell damage consisting of degeneration, single cell necrosis, hyperplasia, karyocytomegaly and atypical nuclei. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although it has been speculated that these toxicities may occur as the result of a species-specific mechanism, experiments which would confirm that theory have not been conducted.

Hepatic Impairment: Patients with moderate non-cirrhotic liver disease need no adjustment of dose. Patients with moderate cirrhotic liver disease have reduced clearance of unbound tolcapone by almost 50%, increasing the average concentration of unbound drug by about twofold. Dosage should be reduced in such patients (see CLINICAL PHARMACOLOGY: *Pharmacokinetics of Tolcapone* and DOSAGE AND ADMINISTRATION). Patients with severe liver impairment should be treated with caution.

Hepatic Enzyme Abnormalities: In phase 3 controlled trials, increases to more than 3 times the upper limit of normal in ALT or AST occurred in approximately 1% of patients at 100 mg tid and 3% of patients at 200 mg tid. Females were more likely than males to have an increase in hepatic enzymes (approximately 5% vs 2%). Approximately one third of patients with elevated enzymes had diarrhea. Increases to more than 8 times the upper limit of normal in hepatic enzymes occurred in 0.3% at 100 mg and 0.7% at 200 mg. Elevated enzymes led to discontinuation in 0.3% and 1.7% of patients treated with 100 mg tid and 200 mg tid, respectively. Elevations usually occurred within 6 weeks to 6 months of starting treatment. In about half the cases with elevated hepatic enzymes, enzyme levels returned to baseline values within 1 to 3 months while patients continued TASMAR treatment. When treatment was discontinued, enzymes generally declined within 2 to 3 weeks but in some cases took as long as 1 to 2 months to return to normal.

One patient, a 55-year old woman who had received treatment with tolcapone 200 mg tid for 53 days, had the onset of diarrhea followed 4 days later by yellowing of the skin and eyes. She died 7 days after the onset of the diarrhea. No liver function tests were performed after the onset of symptoms.

It is recommended that liver enzymes be monitored monthly during the first 3 months of TASMAR treatment, and every 6 weeks for the next 3 months of treatment. Tolcapone should be discontinued for enzyme elevations greater than or equal to 5 times the upper limit of normal or at the appearance of jaundice (see PRECAUTIONS: *Laboratory Tests*).

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Hematuria: The rates of hematuria in placebo-controlled trials were approximately 2%, 4% and 5% in placebo, 100 mg and 200 mg tolcapone, respectively. The etiology of the increase with TASMAR has not always been explained (for example, by urinary tract infection or coumadin therapy). In placebo-controlled trials in the US (N=593) rates of microscopically confirmed hematuria were approximately 3%, 2% and 2% in placebo, 100 mg and 200 mg tolcapone, respectively.

Events Reported With Dopaminergic Therapy: The events listed below are known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists. While cases of Withdrawal Emergent Hyperpyrexia and Confusion have been reported in association with tolcapone withdrawal (see below), the expected incidence of fibrotic complications is so low that even if tolcapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that even a single example would have been detected in a cohort of the size exposed to tolcapone.

Withdrawal Emergent Hyperpyrexia and Confusion: Four cases of a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, and altered consciousness), similar to that reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs, have been reported in association with the abrupt withdrawal or lowering of the dose of tolcapone. In 3 of these cases, CPK was elevated as well. One patient died, and the other 3 patients recovered over periods of approximately 2, 4 and 6 weeks.

Fibrotic Complications: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (eg, tolcapone) that increase dopaminergic activity can cause them is unknown.

Three cases of pleural effusion, one with pulmonary fibrosis, occurred during clinical trials. These patients were also on concomitant dopamine agonists (pergolide or bromocriptine) and had a prior history of cardiac disease or pulmonary pathology (nonmalignant lung lesion).

Information for Patients: Patients should be instructed to take TASMAR only as prescribed.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with TASMAR.

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Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on TASMAR to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with TASMAR.

Patients should be informed that nausea may occur, especially at the initiation of treatment with TASMAR.

Patients should be advised of the possibility of an increase in dyskinesia and/or dystonia.

Although TASMAR has not been shown to be teratogenic in animals, it is always given in conjunction with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS: *Pregnancy*).

Tolcapone is excreted into maternal milk in rats. Because of the possibility that tolcapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Laboratory Tests: It is recommended that transaminases be monitored monthly for the first 3 months of treatment with TASMAR, after which LFTs should be monitored every 6 weeks for the next 3 months. If elevations occur, and a decision is made to continue to treat the patient, more frequent monitoring of complete liver function is recommended. Treatment should be discontinued if ALT exceeds 5 x ULN or if jaundice develops.

Special Populations: Parkinson's disease patients with moderate to severe liver impairment or severe renal impairment should be treated with caution (see DOSAGE AND ADMINISTRATION).

Drug Interactions: *Protein Binding:* Although tolcapone is highly protein bound, in vitro studies have shown that tolcapone at a concentration of 50 μg/mL did not displace other highly protein-bound drugs from their binding sites at therapeutic concentrations. The experiments included warfarin (0.5 to 7.2 μg/mL), phenytoin (4.0 to 38.7 μg/mL), tolbutamide (24.5 to 96.1 μg/mL) and digitoxin (9.0 to 27.0 μg/mL).

Drugs Metabolized by Catechol-O-methyltransferase (COMT): Tolcapone may influence the pharmacokinetics of drugs metabolized by COMT. However, no effects were seen on the pharmacokinetics of the COMT substrate carbidopa. The effect of tolcapone on the pharmacokinetics of other drugs of this class such as α-methyldopa, dobutamine, apomorphine, and isoproterenol has not been evaluated. A dose reduction of such compounds should be considered when they are coadministered with tolcapone.

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Effect of Tolcapone on the Metabolism of Other Drugs: In vitro experiments have been performed to assess the potential of tolcapone to interact with isoenzymes of cytochrome P450 (CYP). No relevant interactions with substrates for CYP 2A6 (coumadin), CYP 1A2 (caffeine), CYP 3A4 (midazolam, terfenadine, cyclosporine), CYP 2C19 (S-mephenytoin) and CYP 2D6 (desipramine) were observed in vitro. The absence of an interaction with desipramine, a drug metabolized by cytochrome P450 2D6, was also confirmed in an in vivo study where tolcapone did not change the pharmacokinetics of desipramine.

Due to its affinity to cytochrome P450 2C9 in vitro, tolcapone may interfere with drugs, whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. However, in an in vivo interaction study, tolcapone did not change the pharmacokinetics of tolbutamide. Therefore, clinically relevant interactions involving cytochrome P450 2C9 appear unlikely. Similarly, tolcapone did not affect the pharmacokinetics of desipramine, a drug metabolized by cytochrome P450 2D6, indicating that interactions with drugs metabolized by that enzyme are unlikely. Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these two drugs are coadministered.

Drugs That Increase Catecholamines: Tolcapone did not influence the effect of ephedrine, an indirect sympathomimetic, on hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise. Since tolcapone did not alter the tolerability of ephedrine, these drugs can be coadministered.

When TASMAR was given together with levodopa/carbidopa and desipramine, there was no significant change in blood pressure, pulse rate and plasma concentrations of desipramine. Overall, the frequency of adverse events increased slightly. These adverse events were predictable based on the known adverse reactions to each of the three drugs individually. Therefore, caution should be exercised when desipramine is administered to Parkinson's disease patients being treated with TASMAR and levodopa/carbidopa.

In clinical trials, patients receiving TASMAR/levodopa preparations reported a similar adverse event profile independent of whether or not they were also concomitantly administered selegiline (a selective MAO-B inhibitor).

Carcinogenesis, Mutagenesis and Impairment of Fertility: *Carcinogenesis:* Carcinogenicity studies in which tolcapone was administered in the diet were conducted in mice and rats. Mice were treated for 80 (female) or 95 (male) weeks with doses of 100, 300 and 800 mg/kg/day, equivalent to 0.8, 1.6 and 4 times human exposure (AUC = 80 ug•hr/mL) at the recommended daily clinical dose of 600 mg. Rats were treated for 104 weeks with doses of 50, 250 and 450 mg/kg/day. Tolcapone exposures were 1, 6.3 and 13 times the human exposure in male rats and 1.7, 11.8 and 26.4 times the human exposure in female rats. There was an increased incidence of uterine adenocarcinomas in female rats at an exposure equivalent to 26.4 times the human exposure. There was evidence of renal tubular injury and renal tubular tumor formation in rats. A low incidence of renal tubular cell adenomas occurred in middle- and high-dose female rats;

tubular cell carcinomas occurred in middle and high dose male and high dose female rats, with a statistically significant increase in high-dose males. Exposures were equivalent to 6.3 (males) or 11.8 (females) times the human exposure or greater; no renal tumors were observed at exposures of 1 (males) or 1.7 (females) times the human exposure. Minimal-to-marked damage to the renal tubules, consisting of proximal tubule cell degeneration, singe cell necrosis, hyperplasia and karyocytomegaly, occurred at the doses associated with renal tumors. Renal tubule damage, characterized by proximal tubule cell degeneration and the presence of atypical nuclei, as well as one adenocarcinoma in a high-dose male, were observed in a 1-year study in rats receiving doses of tolcapone of 150 and 450 mg/kg/day. These histopathological changes suggest the possibility that renal tumor formation might be secondary to chronic cell damage and sustained repair, but this relationship has not been established, and the relevance of these findings to humans is not known. There was no evidence of carcinogenic effects in the long-term mouse study. The carcinogenic potential of tolcapone in combination with levodopa/carbidopa has not been examined.

Mutagenesis: Tolcapone was clastogenic in the in vitro mouse lymphoma/thymidine kinase assay in the presence of metabolic activation. Tolcapone was not mutagenic in the Ames test, the in vitro V79/HPRT gene mutation assay, or the unscheduled DNA synthesis assay. It was not clastogenic in an in vitro chromosomal aberration assay in cultured human lymphocytes, or an in vivo micronucleus assay in mice.

Impairment of Fertility: Tolcapone did not affect fertility and general reproductive performance in rats at doses up to 300 mg/kg/day (5.7 times the human dose on a mg/m^2 basis).

Pregnancy: Pregnancy Category C. Tolcapone, when administered alone during organogenesis, was not teratogenic at doses of up to 300 mg/kg/day in rats or up to 400 mg/kg/day in rabbits (5.7 times and 15 times the recommended daily clinical dose of 600 mg, on a mg/m^2 basis, respectively). In rabbits, however, an increased rate of abortion occurred at a dose of 100 mg/kg/day (3.7 times the daily clinical dose on a mg/m^2 basis) or greater. Evidence of maternal toxicity (decreased weight gain, death) was observed at 300 mg/kg in rats and 400 mg/kg in rabbits. When tolcapone was administered to female rats during the last part of gestation and throughout lactation, decreased litter size and impaired growth and learning performance in female pups were observed at a dose of 250/150 mg/kg/day (dose reduced from 250 to 150 mg/kg/day during late gestation due to high rate of maternal mortality; equivalent to 4.8/2.9 times the clinical dose on a mg/m^2 basis).

Tolcapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa (80/20 mg/kg/day) produced an increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis. Plasma exposures to tolcapone (based on AUC) were 0.5 times the expected human exposure, and plasma exposures to levodopa were 6 times higher than those in humans under therapeutic conditions. In a combination embryo-fetal development study in rats, fetal body weights were reduced by the

combination of tolcapone (10, 30, and 50 mg/kg/day) and levodopa/carbidopa (120/30 mg/kg/day) and by levodopa/carbidopa alone. Tolcapone exposures were 0.5 times expected human exposure or greater: levodopa exposures were 21 times expected human exposure or greater. The high dose of 50 mg/kg/day of tolcapone given alone was not associated with reduced fetal body weight (plasma exposures of 1.4 times the expected human exposure).

There is no experience from clinical studies regarding the use of TASMAR in pregnant women. Therefore, TASMAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: In animal studies, tolcapone was excreted into maternal rat milk.

It is not known whether tolcapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tolcapone is administered to a nursing woman.

Pediatric Use: There is no identified potential use of tolcapone in pediatric patients.

ADVERSE REACTIONS: During the pre-marketing development of tolcapone, two distinct patient populations were studied, patients with end-of-dose wearing-off phenomena and patients with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects. Adverse events are, therefore, shown for these two populations combined.

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials (N=892) associated with the use of TASMAR not seen at an equivalent frequency among the placebo-treated patients were dyskinesia, nausea, sleep disorder, dystonia, dreaming excessive, anorexia, cramps muscle, orthostatic complaints, somnolence, diarrhea, confusion, dizziness, headache, hallucination, vomiting, constipation, fatigue, upper respiratory tract infection, falling, sweating increased, urinary tract infection, xerostomia, abdominal pain, urine discoloration.

Approximately 16% of the 592 patients who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared to 10% of the 298 patients who received placebo. Diarrhea was by far the most frequent cause of discontinuation (approximately 6% in tolcapone patients vs 1% on placebo).

Adverse Event Incidence in Controlled Clinical Studies: Table 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with tolcapone participating in the double-blind, placebo-controlled studies and were numerically more common in at least one of the tolcapone groups. In these studies, either tolcapone or placebo were added to levodopa/carbidopa (or benserazide).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other

factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events incidence rate in the population studied.

Table 4. Summary of Patients With Adverse Events After Start of Trial Drug Administration
(At Least 1% in TASMAR Group and at Least One TASMAR Dose Group > Placebo)

	Placebo	Tolcapone tid	
		100 mg	200 mg
	N = 298	N = 296	N = 298
Adverse Events	(%)	(%)	(%)
Dyskinesia	20	42	51
Nausea	18	30	35
Sleep Disorder	18	24	25
Dystonia	17	19	22
Dreaming Excessive	17	21	16
Anorexia	13	19	23
Cramps Muscle	17	17	18
Orthostatic Complaints	14	17	17
Somnolence	13	18	14
Diarrhea	8	16	18
Confusion	9	11	10
Dizziness	10	13	6
Headache	7	10	11
Hallucination	5	8	10
Vomiting	4	8	10
Constipation	5	6	8
Fatigue	6	7	3
Upper Respiratory Tract Infection	3	5	7
Falling	4	4	6
Sweating Increased	2	4	7
Urinary Tract Infection	4	5	5
Xerostomia	2	5	6
Abdominal Pain	3	5	6
Syncope	3	4	5
Urine Discoloration	1	2	7
Dyspepsia	2	4	3
Influenza	2	3	4
Dyspnea	2	3	3
Balance Loss	2	3	2
Flatulence	2	2	4
Hyperkinesia	1	3	2
Chest Pain	1	3	1
Hypotension	1	2	2
Paresthesia	2	3	1

Adverse Events	N = 298 (%)	100 mg N = 296 (%)	200 mg N = 298 (%)
Stiffness	1	2	2
Arthritis	1	2	1
Chest Discomfort	1	1	2
Hypokinesia	1	1	3
Micturition Disorder	1	2	1
Pain Neck	1	2	2
Burning	0	2	1
Sinus Congestion	0	2	1
Agitation	0	1	1
Bleeding Dermal	0	1	1
Irritability	0	1	1
Mental Deficiency	0	1	1
Hyperactivity	0	1	1
Malaise	0	1	0
Panic Reaction	0	1	0
Tumor Skin	0	1	0
Cataract	0	1	0
Euphoria	0	1	0
Fever	0	0	1
Alopecia	0	1	0
Eye Inflamed	0	1	0
Hypertonia	0	0	1
Tumor Uterus	0	1	0

Other events reported by 1% or more of patients treated with TASMAR but that were equally or more frequent in the placebo group were arthralgia, pain limbs, anxiety, micturition frequency, fractures, vision blurred, pneumonia, paresis, lethargy, asthenia, edema peripheral, gait abnormal, taste alteration, weight decrease and sinusitis.

Effects of Gender and Age on Adverse Reactions: Experience in clinical trials have suggested that patients greater than 75 years of age may be more likely to develop hallucinations than patients less than 75 years of age, while patients over 75 may be less likely to develop dystonia. Females may be more likely to develop somnolence than males.

Other Adverse Events Observed During All Trials in Patients With Parkinson's Disease: TASMAR has been administered in 1536 patients with Parkinson's disease in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of adverse events were grouped into a smaller number of standardized categories using COSTART dictionary terminology. These categories

TASMAR® (tolcapone)

are used in the listing below.

All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events and terms too vague to be meaningful are included, without regard to determination of a causal relationship to TASMAR.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are defined as those occurring in between 1/100 and 1/1000 patients; and rare adverse events are defined as those occurring in fewer than 1/1000 patients.

Nervous System: —frequent: depression, hypesthesia, tremor, speech disorder, vertigo, emotional lability; *infrequent:* neuralgia, amnesia, extrapyramidal syndrome, hostility, libido increased, manic reaction, nervousness, paranoid reaction, cerebral ischemia, cerebrovascular accident, delusions, libido decreased, neuropathy, apathy, choreoathetosis, myoclonus, psychosis, thinking abnormal, twitching; *rare:* antisocial reaction, delirium, encephalopathy, hemiplegia, meningitis.

Digestive System: —frequent: tooth disorder; *infrequent:* dysphagia, gastrointestinal hemorrhage, gastroenteritis, mouth ulceration, increased salivation, abnormal stools, esophagitis, cholelithiasis, colitis, tongue disorder, rectal disorder; *rare:* cholecystitis, duodenal ulcer, gastrointestinal carcinoma, stomach atony.

Body as a Whole: —frequent: flank pain, accidental injury, abdominal pain, infection; *infrequent:* hernia, pain, allergic reaction, cellulitis, infection fungal, viral infection, carcinoma, chills, infection bacterial, neoplasm, abscess, face edema; *rare:* death.

Cardiovascular System: —frequent: palpitation; *infrequent:* hypertension, vasodilation, angina pectoris, heart failure, atrial fibrillation, tachycardia, migraine, aortic stenosis, arrythmia, arteriospasm, bradycardia, cerebral hemorrhage, coronary artery disorder, heart arrest, myocardial infarct, myocardial ischemia, pulmonary embolus; *rare:* arteriosclerosis, cardiovascular disorder, pericardial effusion, thrombosis.

Musculoskeletal System: —frequent: myalgia; *infrequent:* tenosynovitis, arthrosis, joint disorder.

Urogenital System: —frequent: urinary incontinence, impotence; *infrequent:* prostatic disorder, dysuria, nocturia, polyuria, urinary retention, urinary tract disorder, hematuria, kidney calculus, prostatic carcinoma, breast neoplasm, oliguria, uterine atony, uterine disorder, vaginitis; *rare:* bladder calculus, ovarian carcinoma, uterine hemorrhage.

Respiratory System: —frequent: bronchitis, pharyngitis; *infrequent:* cough increased, rhinitis, asthma, epistaxis, hyperventilation, laryngitis, hiccup; *rare:* apnea, hypoxia, lung edema.

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Skin and Appendages: —*frequent:* rash; *infrequent:* herpes zoster, pruritus, seborrhea, skin discoloration, eczema, erythema multiforme, skin disorder, furunculosis, herpes simplex, urticaria.

Special Senses: —*frequent:* tinnitus; *infrequent:* diplopia, ear pain, eye hemorrhage, eye pain, lacrimation disorder, otitis media, parosmia; *rare:* glaucoma.

Metabolic and Nutritional: — *infrequent:* edema, hypercholesteremia, thirst, dehydration.

Hemic and Lymphatic System: — *infrequent:* anemia; *rare:* leukemia, thrombocytopenia.

Endocrine System: — *infrequent:* diabetes mellitus.

Unclassified: — *infrequent:* surgical procedure.

DRUG ABUSE AND DEPENDENCE: Tolcapone is not a controlled substance.

Studies conducted in rats and monkeys did not reveal any potential for physical or psychological dependence. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

OVERDOSAGE: The highest dose of tolcapone administered to humans was 800 mg tid, with and without levodopa/carbidopa coadministration. This was in a 1-week study in elderly, healthy volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 μg/mL (compared to 3 μg/mL and 6 μg/mL with 100 mg and 200 mg tolcapone, respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa/carbidopa.

The threshold for the lethal plasma concentration for tolcapone based on animal data is >100 μg/mL. Respiratory difficulties were observed in rats at high oral (gavage) and intravenous doses and in dogs with rapidly injected intravenous doses.

Management of Overdose: Hospitalization is advised. General supportive care is indicated. Based on the physicochemical properties of the compound, hemodialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: Therapy with TASMAR may be initiated with 100 mg or 200 mg tid, always as an adjunct to levodopa/carbidopa therapy. Although clinical trial data suggest that initial treatment with 200 mg tid (a daily dose of 600 mg) is reasonably well tolerated, the prescriber may wish to begin treatment with 100 mg tid because of the potential for increased dopaminergic side effects (eg, dyskinesias) and the possible necessary adjustment of the concomitant levodopa/carbidopa dose. In clinical trials, the first dose of the day of TASMAR was always taken together with the first dose of the day of levodopa/carbidopa, and the subsequent doses of TASMAR were given approximately 6 and 12 hours later.

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In clinical trials, the majority of patients required a decrease in their daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias before beginning treatment.

The maximum recommended dose of TASMAR is 600 mg a day, given as tid dosing. To optimize an individual patient's response, reductions in daily levodopa dose may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 30% in those patients requiring a levodopa dose reduction. (Greater than 70% of patients with levodopa doses above 600 mg daily required such a reduction.)

The safety and effectiveness of daily doses greater than 600 mg, or of single doses greater than 200 mg, have not been systematically evaluated.

TASMAR can be combined with both the immediate and sustained release formulations of levodopa/carbidopa.

TASMAR may be taken with or without food (see CLINICAL PHARMACOLOGY).

Patients With Impaired Renal or Hepatic Function: Patients with moderate to severe cirrhosis of the liver should not be escalated to 200 mg TASMAR tid (see CLINICAL PHARMACOLOGY).

No dose adjustment of TASMAR is recommended for patients with mild to moderate renal impairment. The safety of tolcapone has not been examined in subjects who had creatinine clearance less than 25 mL/min (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED: TASMAR is supplied as film-coated tablets containing 100 mg or 200 mg tolcapone. The 100 mg beige tablet and the 200 mg reddish-brown tablet are hexagonal and biconvex. Imprinted with black ink on one side of the tablet is TASMAR and the tablet strength (100 or 200), on the other side is ROCHE.

TASMAR 100 mg Tablets: bottles of 90 (NDC 0004-5920-01) and bottles of 500 (NDC 0004-5920-14).

TASMAR 200 mg Tablets: bottles of 90 (NDC 0004-5921-01) and bottles of 500 (NDC 0004-5921-14).

Storage: Store at controlled room temperature 20° to 25°C (68° to 77°F) in tight containers as defined in USP/NF.

TASMAR® (tolcapone)

(Roche Hexagon)

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

25703287-0198

Issued: January 1998
Printed in USA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-697

Hoffman-La Roche Inc.
Attention: Thomas Watson
340 Kingsland Street
Nutley, New Jersey 07110-1199

JAN 29 1998

Dear Mr. Watson:

Please refer to your new drug application dated June 03, 1996, and your resubmission dated July 28, 1997 and received July 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tasmar (tolcapone) 100 mg & 200 mg tablets.

We acknowledge receipt of your submissions dated:

July 30, 1997
October 21, 1997
September 2, 1997
December 5, 1997
September 12, 1997

The User Fee goal date for this application is January 30, 1998.

This new drug application provides for the following indication:

Tasmar™ is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of Tasmar™ was demonstrated in randomized controlled trials in patients receiving concomitant levodopa therapy with carbidopa or another aromatic amino acid decarboxylase inhibitor who experienced end of dose wearing-off phenomena as well as in patients who did not experience such phenomena.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

We remind you that Tasmar has been approved for a product expiration date of 24 months.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or

US005236952A

United States Patent [19]

Bernauer et al.

[11] Patent Number: 5,236,952

[45] Date of Patent: Aug. 17, 1993

[54] CATECHOL DERIVATIVES

[75] Inventors: Karl Bernauer, Oberwil; Janos Borgulya, Basel; Hans Bruderer, Biel-Benken; Mosé DaPrada, Riehen; Gerhard Zürcher, Basel, all of Switzerland

[73] Assignee: Hoffmann-La Roche Inc., Nutley, N.J.

[21] Appl. No.: 686,210

[22] Filed: Apr. 16, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 395,110, Aug. 16, 1989, abandoned, which is a continuation of Ser. No. 22,891, Mar. 6, 1987, abandoned.

[30] **Foreign Application Priority Data**

Mar. 11, 1986 [CH] Switzerland 980/86
Jan. 9, 1987 [CH] Switzerland 62/87

[51] **Int. Cl.**[5] **A61K 31/275**
[52] **U.S. Cl.** **514/520**; 514/523; 514/525; 514/676; 568/306; 558/415
[58] **Field of Search** 568/306; 558/415, 520, 558/525; 514/676, 523

[56] **References Cited**

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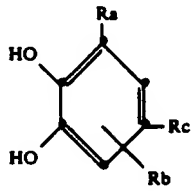
(List continued on next page.)

Primary Examiner—James H. Reamer
Attorney, Agent, or Firm—George M. Gould; George W. Johnston; Ellen Ciambrone Coletti

[57] ABSTRACT

Catechol derivatives of the formula



Ia

wherein Ra, Rb and Rc have the significance given herein,

the ester and ether derivatives thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof are described and possess valuable pharmacological properties. In particular, they inhibit the enzyme catechol-O-methyltransferase (COMT), a soluble, magnesium-dependent enzyme which catalyses the transference of the methyl group of S-adensoylmethionine to a catechol substrate, whereby the corresponding methyl ethers are formed. Suitable substrates which can be O-methylated by COMT and which can thus be deactivated are, for example, extraneuornal catecholamines and exogeneously-administered therapeutically active substances having a catechol structure.

Formula Ia above embraces not only compounds which form part of the invention, but also known compounds; the compounds which form part of the invention can be prepared according to known methods.

22 Claims, No Drawings

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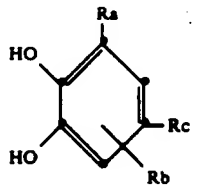
CATECHOL DERIVATIVES

This is a continuation of application Ser. No. 395,110, filed Aug. 16, 1989 now abandoned, which is a continuation of Ser. No. 07/022,891, filed Mar. 6, 1987, now abandoned.

BRIEF SUMMARY OF THE INVENTION

The invention relates to catechol derivatives of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group $-(A)_n-(Q)_m-R^1$ or $-(A)_n-Q-R^2$, A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1, R^1 is the group $-COR^3$, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom, R^2 is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R^3 is hydroxy, amino, an optionally substituted, saturated or partially unsaturated, lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group —CO— or $>C=N-(Z-)_p-R^4$, Z is an oxygen atom or an imino group, P is the integer 0 or 1 and R^4 is hydrogen or saturated or partially unsaturated, lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,

the ester and ether derivatives thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof. The compounds of formula Ia possess valuable pharmacological properties. In particular, these compounds inhibit the enzyme catechol-O-methyltransferase (COMT), a soluble, magnesium-dependent enzyme which catalyzes the transference of the methyl group of S-adenosylmethionine to a catechol substrate, whereby the corresponding methyl ethers are formed. Suitable substrates which can be O-methylated by COMT and which can thus be deactivated are, for example, extraneuronal catecholamines and exogeneously-administered therapeutically active substances having a catechol structure.

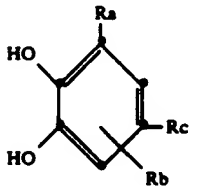
The compounds of formula Ia above can accordingly be used in the prevention or control of illnesses in which a deactivation of extraneuronal catecholamines by COMT plays a role, for example, in the prevention or control of depressions. In this case the compounds of formula Ia above can be used as individual compounds or in combination with other therapeutically active substances which favorably influence the course of the illness. The compounds of formula Ia can, however, also be used as co-medications with other therapeutically active substances.

The compounds of formula Ia can, however, also be used to improve the prevention or control of illnesses

with therapeutically active substances which have a catechol structure. The treatment of Parkinson's disease and of parkinsonism with L-dopa, a therapeutically active substance having the catechol structure, can be mentioned as an example. In such cases the compounds of formula Ia can be used in the form of a co-medication or as combination preparations.

The field of diagnostics offers a further possibility for the use of the compounds of formula Ia above. After the administration of [^{18}F]-6-fluoro-L-dopa, [^{18}F]-dopamine in the brain can be visualized with the aid of positron emission tomography. By adding a compound of formula Ia above, the COMT is inhibited and thus the formation of [^{18}F]-3-O-methyldopa is prevented. In the absence of a COMT-inhibitor, the [^{18}F]-3-O-methyldopa would penetrate into the brain and lead to a greatly increased background which would made the diagnosis very much more difficult.

DETAILED DESCRIPTION OF THE INVENTION



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group $-(A)_n-(Q)_m-R^1$ or $-(A)_n-Q-R^2$, A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1 R^1 is the group $-COR^3$, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom, R^2 is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R^3 is hydroxy, amino, an optionally substituted, saturated or partially unsaturated, lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group —CO— or $>C=N-(Z-)_p-R^4$, Z is an oxygen atom or an imino group, P is the integer 0 or 1 and R^4 is hydrogen or saturated or partially unsaturated, lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,

including the ester and derivatives thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof. The compounds of formula Ia possess valuable pharmacological properties. In particular, these compounds inhibit the enzyme catechol-O-methyltransferase (COMT), a soluble, magnesium-dependent enzyme which catalyzes the transference of the methyl group of S-adenosylmethionine to a catechol substrate, whereby the corresponding methyl ethers are formed. Suitable substrates which can be O-methylated by COMT and which can thus be deactivated are, for example, extraneuronal catecholamines and exogeneously-administered therapeutically active substances having a catechol structure.

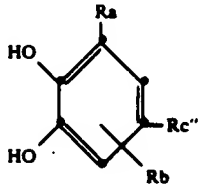
The compounds of formula Ia above can accordingly be used in the prevention or control of illnesses in which

a deactivation of extraneuronal catecholamines by COMT plays a role, for example, in the prevention or control of depressions. In this case the compounds of formula Ia above can be used as individual compounds or in combination with other therapeutically active substances which favorably influence the course of the illness. The compounds of formula Ia can, however, also be used as co-medications with other therapeutically active substances.

The compounds of formula Ia can, however, also be used to improve the prevention or control of illnesses with therapeutically active substances which have a catechol structure. The treatment of Parkinson's disease and of parkinsonism with L-dopa, a therapeutically active substance having the catechol structure, can be mentioned as an example. In such cases the compounds of formula Ia can be used in the form of a co-medication or as combination preparations.

The field of diagnostics offers a further possibility for the use of the compounds of formula Ia above. After the administration of [^{18}F]-6-fluoro-L-dopa, [^{18}F]-dopamine in the brain can be visualized with the aid of positron emission tomography. By adding a compound of formula Ia above, the COMT is inhibited and thus the formation of [^{18}F]-3-O-methyldopa is prevented. In the absence of a COMT-inhibitor, the [^{18}F]-3-O-methyldopa would penetrate into the brain and lead to a greatly increased background which would made the diagnosis very much more difficult.

Formula Ia above embraces not only known, but also compounds which form part of the invention. The compounds of formula Ia which are known fall under the formula

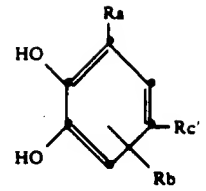


Ia'

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc" is nitro, cyano or the group —(A)$_n$—COOH or —(A)$_n$—Q—H, A is vinylene optionally substituted by lower alkyl, n is the number 0 or 1, Q is the group —CO— or >C=N—(Z)$_p$—R^4, Z is an oxygen atom or an imino group, p is the number 0 of 1 and R^4 is hydrogen or a saturated or partially unsaturated lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group, with the proviso that Ra is nitro when Rc" is cyano or nitro,

and ester and ether derivatives thereof which are hydrolyzable under phydiological conditions and the pharmaceutically acceptable salts thereof.

The compounds of formula Ia which form part of the invention are the compounds of the formula



Ib

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc' is nitro, cyano or the group —(A)$_n$—(Q)$_m$—R^{11} or —(A)$_n$—Q—R^{21}, A is vinylene optionally substituted by lower alkyl, n is the number 0 or 1, m is the number 0 or 1, R^{11} is the group —COR^{31}, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom, R^{21} is an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R^{31} is hydroxy, amino, an optionally substituted, saturated or partially unsaturated, lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group —CO— or >C=N—(Z)$_p$—R^4, Z is an oxygen atom or an imino group, P is the number 0 or 1 and R^4 is hydrogen or saturated or partially unsaturated, lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group, with the proviso that Ra is cyano when Rc' is cyano or nitro and R^{31} has a significance different from hydroxy when m is the number 0,

and the ester and ether derivatives thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof.

Objects of the invention are: The above compounds of formula Ia and the mentioned derivatives thereof for use as therapeutically active substances; medicaments based on these compounds and derivatives; the preparation of such medicaments; the use of the compounds and derivatives in question in the prevention or control of illnesses; the use of the compounds and derivatives in question for the preparation of medicaments which in a given case inhibit the enzyme COMT in the sense of a desired side-effect; the compounds of formula Ib above and the mentioned derivatives thereof; the preparation of these compounds and derivatives; as well as intermediates for their preparation.

The term "lower" denotes residues and compounds with a maximum of 7, preferably a maximum of 4, carbon atoms. The term "alkyl", taken along or in combinations, such as, "alkyl group", "alkoxy", "alkylthio" and "alkylimino", denotes straight-chain or branched, saturated hydrocarbon residues, for example, such as methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, i-butyl, t-butyl and the like. The term "saturated or partially unsaturated lower hydrocarbon residue" denotes open-chain and cyclic groups and combinations thereof. Examples of saturated and partially unsaturated lower hydrocarbon residues are: lower alkyl groups such as those defined above; lower alkenyl groups, for example, 2-propenyl, 2-butenyl, 3-butenyl and 2-methyl-2-propenyl; C$_{3-7}$-cycloalkyl and C$_{8-10}$-bicycloalkyl groups optionally substituted by lower alkyl groups, for example, cyclopropyl, cyclopentyl, 2-methylcyclopentyl, cyclohexyl and 3-methylcyclohexyl; lower cycloalkenyl

groups optionally substituted by lower alkyl groups, for example, 3-cyclopentenyl, 1-methyl-3-cyclopentenyl and 3-cyclohexenyl; lower alkyl or alkenyl groups substituted by lower cycloalkyl or cycloalkenyl groups, for example, cyclopropylmethyl, cyclopropylethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl and 3-cyclopropyl-2-propenyl. The lower alkenyl groups preferably contain 2–4 carbon atoms; the cycloalkyl and cycloalkenyl groups preferably contain 3–6 carbon atoms.

The following come into consideration as substituents for the above lower hydrocarbon residues: Hydroxy, cyano, nitro, halogen, amino, lower alkylamino, di(lower alkyl)-amino, lower alkoxy, lower alkoxycarbonyl, aryl, arylaminocarbonyl, arylcarbonyl, arylcarbonylamino, lower alkanoyloxy, lower alkanoyl, carbamoyl, mono- or di(lower alkyl)carbamoyl, lower alkylenedioxy, trifluoromethyl, carboxy, lower alkanoylamino, lower alkoxycarbonylamino and lower alkylthio. The saturated or partially unsaturated lower hydrocarbon residues are preferably unsubstituted or mono- or disubstituted.

The term "aryl" denotes carbocyclic aromatic groups, preferably mono- or bicyclic groups. Especially preferred carbocyclic aromatic groups are phenyl and naphthyl, especially phenyl. These groups are optionally substituted by: halogen, trifluoromethyl, nitro, amino, mono- or di(lower alkyl)amino, lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyl, lower alkoxycarbonyl, carboxy, hydroxy, cyano, lower alkanoyloxy, carbamoyl, mono- or di(lower alkyl)carbamoyl, lower alkylenedioxy, lower alkanoylamino or lower alkoxycarbonylamino. The carbocyclic aromatic groups are preferably unsubstituted or mono- or disubstituted.

The term "aromatic or partially unsaturated heterocyclic group" preferably denotes a mono-, di- or tricyclic, aromatic or partially unsaturated, heterocyclic group with up to 5 hetero atoms from the group consisting of nitrogen, sulfur and oxygen. The heterocyclic groups preferably contain 1–4 nitrogen atoms and/or an oxygen or sulfur atom. They are preferably mono- or bicyclic. The hetero atoms are preferably distributed on one or two rings, whereby nitrogen atoms can simultaneously also be components of 2 rings. The heterocyclic groups are preferably aromatic. They can be substituted and are preferably mono-, di- or trisubstituted. As substituents there come into consideration: halogen, trifluoromethyl, nitro, carboxy, amino, arylamino, lower alkyl, lower alkoxy, hydroxy, lower alkoxycarbonyl, lower alkanoyl, lower alkanoyloxy, oxo, lower alkylenedioxy, mercapto, lower alkylthio, lower alkylamino, di(lower alkyl)amino, C_{3-7}-cycloalkylamino, C_{8-10}-bicycloalkylamino, lower alkanoylamino, lower alkoxycarbonylamino, carbamoyl, mono- or di(lower alkyl)carbamoyl, cyano, aryl, aryl-lower alkyl, aryl-lower alkylamino, heteroaryl, heteroaryl-lower alkyl, heteroarylamino and C_{3-7}-cycloalkyl. The monocyclic heterocyclic groups are preferably 5- or 6-membered and contain a maximum of four hetero atoms. The bicyclic heterocyclic groups are preferably 8- to 10-membered, with the individual rings being preferably 5- or 6-membered.

The following are to be mentioned as examples of such heterocyclic groups: Pyridyl, pyrazinyl, triazinyl, thiadiazinyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, tetrazolyl, imidazolyl, thienyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, benzoxazinyl, quinoxalinyl, benzopyranyl, benzimidazolyl, indolyl, imidazothiazolyl, imidazothiadiazolyl, imidazopyridyl, benzothiazinyl, benzoquinoxalinyl and imidazobenzothiazolyl.

The term "heteroaryl" denotes aromatic heterocyclic groups, as defined above.

The term "a saturated, N-containing heterocyclic group attached via a ring nitrogen atom" preferably denotes a 3- to 7-membered, preferably 4- to 6-membered, saturated N-heterocycle which, in addition to the said nitrogen atom, can contain an oxygen, sulfur or nitrogen atom as a second hetero atom. These saturated N-heterocycles can be mono- or disubstituted by: lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, lower hydroxyalkyl, lower alkoxyalkyl, lower alkanoyloxyalkyl, lower alkoxycarbonyl, lower alkanoyl, carbamoyl, mono- or di(lower alkyl)carbamoyl, oxo and/or lower alkylenedioxy.

The following are to be mentioned as examples of such N-containing heterocyclic groups: 4-morpholinyl, 1-pyrrolidinyl and 1-azetidinyl.

The ester and ether derivatives which are hydrolyzable under physiological conditions are preferably compounds of formula Ia in which at least one of the two phenolic hydroxy groups is acylated by a lower fatty acid or etherified by a lower 1-alkoxycarbonyloxy-1-alkyl, lower 1-alkanoyloxy-1-alkyl or by a lower 2-oxo-1-alkyl group.

The substituent Ra preferably is nitro. The substituent Rb is preferably situated in the p-position to the substituent Ra and preferably is hydrogen, chlorine or fluorine, with hydrogen being especially preferred. The substituent Rc' preferably is the group —CO—R^{11} in which R^{11} is an aromatic, mononuclear carbocyclic group or an aromatic, mononuclear heterocyclic group with 1–3 nitrogen atoms as the hetero ring member(s) which is attached via a carbon atom. In an especially preferred embodiment R^{11} is a phenyl group optionally mono- or disubstituted by halogen, trifluoromethyl, cyano, hydroxy or lower alkyl, or a pyridyl group.

Particularly preferred compounds of the invention are:

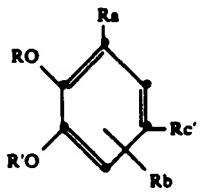
3,4-Dihydroxy-5-nitrobenzophenone,

2'-fluoro-3,4-dihydorxy-5-notribenzophenone and

3,4-dihydroxy-5-nitrophenyl 4-pyridyl ketone.

The compounds of formula Ib, the ester and ether derivatives thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof can be prepared in accordance with the invention by

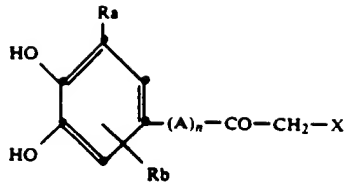
a) cleaving the lower alkyl ether group(s) in a compound of the formula



II

wherein one of the symbols R and R' is lower alkyl and the other is hydrogen or lower alkyl and Ra, Rb and Rc' have the above significance, or

b) reacting a compound of the formula

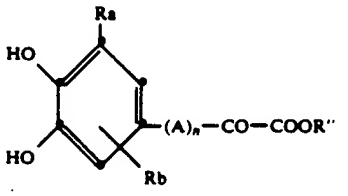


Ib¹

wherein X is a leaving group and Ra, Rb, A and n have the above significance,

with a thioamide, thiourea, thiocarboxylic acid hydrozide, thiosemicarbozide, amidine, guanidine, amidrazone, aminoguanidine, cyclic amidine, 1,2-diamine, 1,2-aminothiol or a 1,2-aminoalcohol and, if desired, dehydrogenating the cyclocondensation product obtained or

c) reacting a compound of the formula



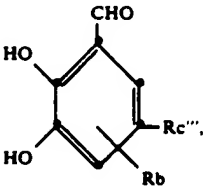
Ib²

wherein R'' is lower alkyl and Ra, Rb, A and n have the above significance,

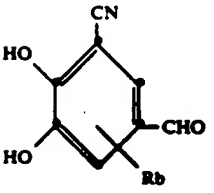
with a 1,2-diamine, 1,2-aminothiol, 1,2-aminoalcohol, semicarbazide, thiosemicarbazide, amidrazone or an aminoguanidine and, if desired, dehydrogenating the cyclocondensation product obtained, or

d) reacting a compound of formula Ib¹ above with a β-aminocarbonyl compound, or

e) converting the carboxaldehyde group(s) in a compound of the formula

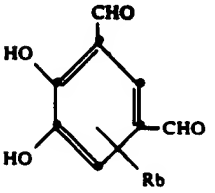


III



Ia²

or

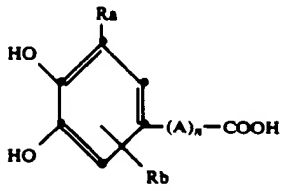


IV

wherein Rc'', is nitro, cyano or the group —(A)$_n$—R^{12} and R^{12} is the group —COR^{31}, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom and Ra, Rb, A, n and R^{31} have the above significance,

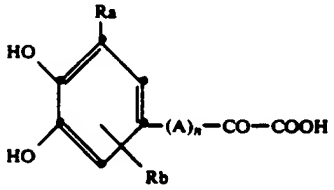
or in a di-O-lower alkanoyl derivative thereof into the cyano group(s), or

f) reacting a di-O-lower alkanoyl derivative of a carboxylic acid of the formula



Ia³

or



Ib³

wherein Ra, Rb, A and n have the above significance, in the presence of a condensation agent or a reactive derivative or a di-O-lower alkanoyl derivative of a carboxylic acid of formula Ia³ or Ib³ with a compound of the formula

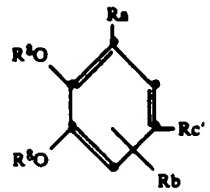
V

or

VI

wherein R^5 is an optionally substituted, saturated or partially unsaturated, lower hydrocarbon residue, R^6 is hydrogen or lower alkyl and R^7 is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue or R^6 and R^7 taken together with the nitrogen atom signify a saturated N-containing heterocyclic group, or

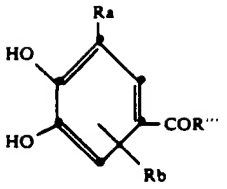
g) hydrolyzing a compound of formula Ib² or a compound of the formula



Ib⁴

wherein R^8 is lower alkanoyl and Ra, Rb and Rc have the above significance,

h) reacting a compound of the formula



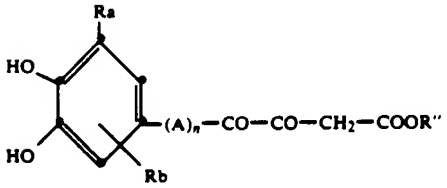
Ib⁵

wherein Ra and Rb have the above significance and R''' is hydrogen or lower alkyl, or a di-O-lower alkanoyl derivative thereof in the presence of a secondary amine with a compound of the formula

$$CH_3CO-R^{23} \qquad \text{VII}$$

wherein R^{23} is an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, or

i) reacting a compound of the formula



Ib⁶

wherein Ra, Rb, A, n and R'' have the above significance,

with a hydrazine or an amidine, or

j) reacting a compound of formula Ib above in which m is the integer 1 and Q is the group —CO— with a compound of the formula

$$H_2N-(Z)_p-R^4 \qquad \text{VIII}$$

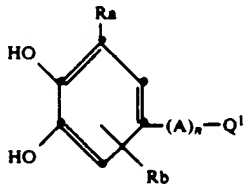
wherein Z, p and R^4 have the above significance, and, if desired,

k) converting a compound of formula Ib above into an ester or ether derivative which is hydrolyzable under physiological conditions or into a pharmaceutically acceptable salt thereof.

In accordance with process variant a) the compounds of formula Ib can be prepared by cleaving the ether group(s) in a compound of formula II. This ether cleavage can be carried out according to known methods which are familiar to any person skilled in the art. The ether cleavage can be carried out, for example, by treatment with hydrogen bromide in a suitable solvent. Suitable solvents are, for example, water, acetic acid and mixtures thereof. The reaction is preferably carried out at an elevated temperature, for example in a temperature range of about 100° C. to the boiling temperature of the reaction mixture. There are preferably used 48 percent hydrobromic acid or mixtures thereof with acetic acid.

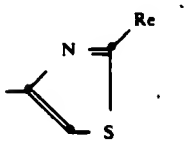
The ether cleavage can also be carried out by treatment with boron tribromide in a suitable solvent at temperatures of about −60° C. to about room temperature. Suitable solvents are especially halogenated lower hydrocarbons, such as, methylene chloride, chloroform and the like. Other suitable methods are: treatment with pyridinium hydrochloride at temperatures of about 150° C. to about 250° C. and treatment with sodium iodide/-solicon tetrachloride in an inert organic solvent at an elevated temperature, for example, at the reflux temperature of the reaction mixture. Suitable solvents for the latter process are, for example, acetonitrile, aromatic hydrocarbons, such as, benzene or toluene, mixtures thereof and the like.

In accordance with process variant b) there can be prepared compounds of the formula

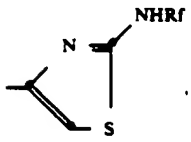


Ib⁷

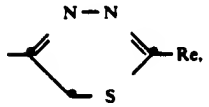
wherein Ra, Rb, A and n have the above significance and Q^1 is a group of the formula



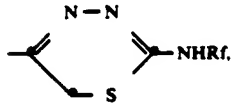
(a)



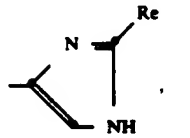
(b)



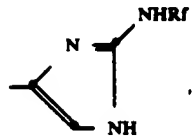
(c)



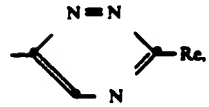
(d)



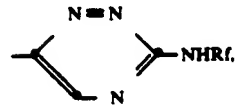
(e)



(f)



(g)

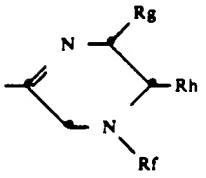


(h)

-continued

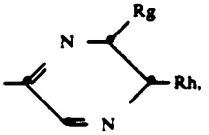
(i)

(k)

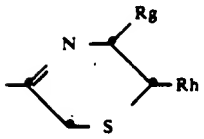


or

(k')

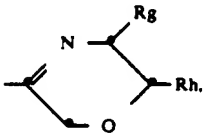


(l)



or

(m)

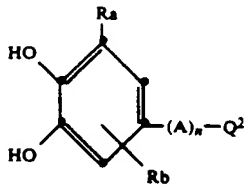


in which Re is hydrogen, C_{3-7}-alkyl, C_{3-7}-cycloalkyl, aryl, heteroaryl, aryl-lower alkyl or heteroaryl-lower alkyl, Rf is hydrogen, aryl, aryl-lower alkyl, lower alkyl, lower alkoxycarbonyl, heteroaryl, heteroaryl-lower alkyl, C_{8-10}-bicycloalkyl or C_{3-7}-cycloalkyl, Rg and Rh each are independently hydrogen, cyano, lower alkyl, C_{3-7}-cycloalkyl, aryl, aryl-lower alkyl, heteroaryl or heteroaryl-lower alkyl or Rg and Rh taken together with the two carbon atoms to which they are attached are an aromatic carboxycyclic group, or an aromatic or partially unsaturated heterocyclic group, the dotted line is an optional bond and Q^4 taken together with the carbon atom and the nitrogen atom signify an aromatic or partially unsaturated, heterocyclic group which contains at least one nitrogen atom as a hetero ring member.

Suitable solvents for this process aspect are lower alcohols such as ethanol, n-butanol, n-hexanol and ethylene glycol, open-chain and cyclic ethers which can contain free hydroxy groups, for example, tetrahydrofuran, dioxane, t-butyl methyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, ethylene glycol monomethyl ether and diethylene glycol monomethyl ether, acetonitrile, dimethylformamide, dimethylacetamide and dimethyl sulfoxide. The desired reaction can also be carried out without a solvent by dry heating the reaction partners. The reaction is preferably carried out an at elevated temperature, for example, in a range of about 50° C. to 150° C., whereby it is preferably carried out at the boiling temperature of the solvent insofar as it is carried out in the presence of a solvent and the boiling point lies in the previously mentioned range.

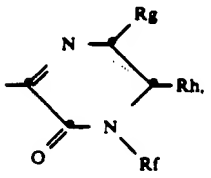
In accordance with process variant c) there can be prepared compounds of the formula

Ib^g

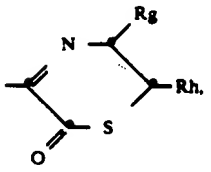


in which Ra, Rb, A and n have the above significance and Q^2 is a group of the formula

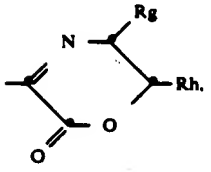
(n)



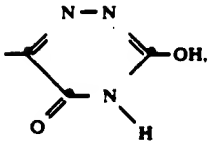
(o)



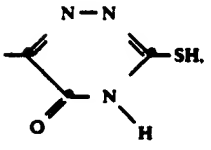
(p)



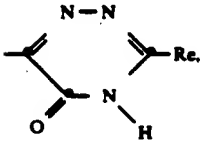
(q)



(r)



(s)



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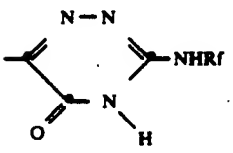
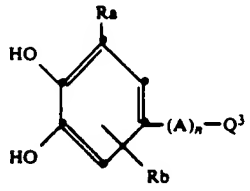


in which Re, Rf, Rg, Rh and the dotted line have the above significance.

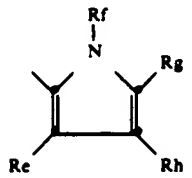
The reaction in accordance with process variant c) can be carried out under the same reaction conditions as process variant b).

In accordance with process variant d) there can be prepared compounds of the formula



Ib⁹

wherein Q^3 is the group of the formula



(u)

and Ra, Rb, Re, Rf, Rg, Rh, A, n and the dotted line have the above significance.

Process variant d) can also be carried out under the same reaction conditions as process variant b).

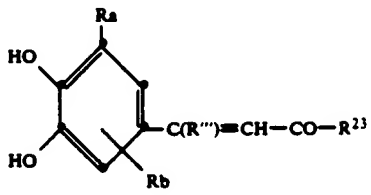
In accordance with process variant e) there can be prepared compounds of formula Ib in which Ra is cyano, Rc' is nitro, cyano or the group —$(A)_n$—R^{12} and R^{12} is the group —COR^{31}, an aromatic carbocyclic group or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom and Rb, A, n and R^{31} have the above significance. The conversion of the carboxaldehyde group(s) into the cyano group(s) can be effected according to known methods which are familiar to any person skilled in the art. For example, a compound of formula Ia^2. III or IV can be treated with hydroxylamine O-sulfonic acid at an elevated temperature, with water being preferably used as the solvent. The reaction can be carried out in a temperature range of about 50° C. to about 100° C.

In accordance with process variant f) there can be prepared di-O-lower alkanoyl derivatives of compounds of formula Ib in which Rc' is the group —$(A)_n$—$(CO)_m$—COR^{32} and R^{32} is amino, an optionally substituted, saturated or partially unsaturated, lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocylic group attached via a ring nitrogen atom and A, n and m have the above significance. This reaction can also be carried out according to known methods which are familiar to any person skilled in the art. Lower alkyl esters can be prepared, for example, by treating the carboxylic acid with the corresponding lower alcohol in the presence of an acid, with the corresponding lower alcohol being preferably used as the solvent. Suitable acids are, for example, mineral acids such as hydrogen chloride and organic sulfonic acids such as p-toluenesulfonic acid. The reaction temperature preferably lies in a range of room temperature to the boiling temperature of the chosen solvent.

The remaining esters and the amides are preferably prepared starting from reactive carboxylic acid derivatives. Suitable reactive carboxylic acid derivatives are, for example, the corresponding carboxylic acid halides, especially the carboxylic acid chlorides, corresponding carboxylic acid anhydrides and mixed anhydrides, for example, with trifluoroacetic acid and organic sulfonic acids such as mesitylenesulfonic acid and p-toluenesulfonic acid, corresponding carboxylic acid imidazolides and the like. The reaction is conveniently carried out in the presence of an acid-binding agent and in an inert organic solvent. Suitable acid-binding agents are, for example, tertiary amines such as triethylamine and pyridine. In the preparation of amides, excess amine of formula VI can also be used as the acid-binding agent. Suitable solvents are, for example, open-chain and cyclic ethers such as tetrahydrofuran, diethyl ether, t-butyl methyl ether, dioxane, ethylene glycol, dimethyl ether or the like, halogenated hydrocarbons such as methylene chloride, chloroform and 1,2-dichloroethane, acetonitrile and dimethylformamide.

The hydrolysis of compounds of formula Ib^4 to the corresponding catechol derivatives in accordance with process variant g) can also be carried out according to known methods which are familiar to any person skilled in the art. The hydrolysis can be carried out, for example, by treatment with an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide in a suitable solvent. Suitable solvents are, for example, lower alcohols such methanol and water or mixtures thereof. The hydrolysis can be carried out, for example, in a temperature range of about 0° C. to the boiling temperature of the solvent. However, it is preferably carried out at room temperature.

In accordance with process variant h) there can be prepared compounds of the formula

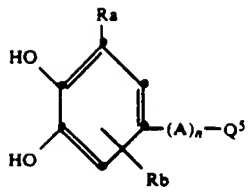


Ib^{10}

wherein Ra, Rb R''' and R^{23} have the above significance,

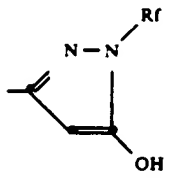
and the corresponding di-O-lower alkanoyl derivatives thereof. Cyclic amines such as pyrrolidine, piperidine, morpholine and thiomorpholine are preferably used as the secondary amine. Suitable solvents for this process are, for example, open-chain and cyclic ethers such as tetrahydrofuran, diethyl ether, t-butyl methyl ether, dioxane, ethylene glycol and dimethyl ether, halogenated hydrocarbons such as methylene chloride, chloroform and 1,2-dichloroethane, acetonitrile and dimethylformamide. The reaction temperature conveniently lies in a range of about 0° C. to the boiling temperature of the chosen solvent. The reaction is preferably carried out at room temperature. In an especially preferred embodiment the reaction is carried out in the presence of an acid, preferably a carboxylic acid such as acetic acid.

In accordance with process variant i) there can be prepared compounds of the formula



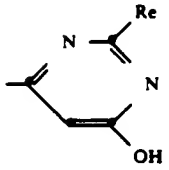
Ib[11]

wherein Q^5 is the group



(v)

or

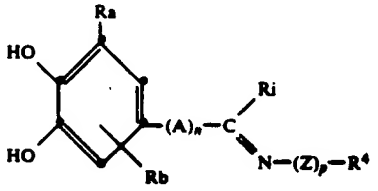


(w)

and Ra, Rb, Re, Rf, A and n have the above significance.

Suitable solvents for this process are, for example, lower alcohols such as methanol and ethanol, open-chain and cyclic ethers such as tetrahydrofuran, diethyl ether, t-butyl methyl ether, dioxane, ethylene glycol and dimethyl ether, acetonitrile and dimethylformamide. The reaction is preferably carried out at an elevated temperature, for example in a range of about 50° C. to the boiling temperature of the chosen solvent. It is preferably carried out at the boiling temperature of the chosen solvent.

In accordance with process variant j) there can be prepared compounds of the formula



Ib[12]

wherein Ri is the group —COR^{31}, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue and Ra, Rb, R^{31}, R^4, A, Z, n and p have the above significance.

This process can also be carried out according to know methods which are familiar to any person skilled in the art. Suitable solvents are, for example, lower alcohols such as methanol and ethanol, dimethylformamide and water. The reaction is conveniently carried out at room temperature.

In accordance with process variant k), the compounds of formula Ib can be converted into ester or ether derivatives which are hydrolyzable under physiological conditions. Suitable ester derivatives which are hydrolyzable under physiological conditions are especially the compounds of formula Ib in which ate last one of the two phenolic hydroxy groups is acylated by a lower fatty acid. These can be prepared according to known methods which are familiar to any person skilled in the art. In a preferred embodiment, the acylation is carried out with the corresponding lower fatty acid anhydride in the presence of a catalytic amount of a strong acid, with excess fatty acid anhydride being preferably used as the solvent. Suitable acids are, for example, sulfuric acid and organic sulfonic acids such as p-toluenesulfonic acid.

Suitable ether derivatives which are hydrolyzable under physiological conditions are, for example, compounds of formula Ib in which at least one of the two phenolic hydroxy groups is etherified by a lower 1-alkoxycarbonyl-oxy-1-alkyl, lower 1-alkanoyloxy-1-alkyl or by a lower 2-oxo-1-alkyl group. The etherification can be carried out according to known methods which are familiar to any person skilled in the art. For example, a compound of formula Ib can be reacted with a lower 1-alkoxycarbonyloxy-1-alkyl halide, a lower 1-alkanoyloxy-1-alkyl halide or a lower 2-oxo-1-alkyl halide, with this etherification being conveniently carried out in the presence of a base. As halides there come into consideration, in particular, the iodides. Suitable bases are, for example, alkali metal hydroxides and alkali metal carbonates such as sodium hydroxide and sodium carbonate.

In accordance with process variant k), compounds of formula Ib above can also be converted into pharmaceutically acceptable salts. As salts there come into consideration, in particular, salts with pharmaceutically acceptable bases. As examples of such salts there are to be mentioned the alkali metal salts such as the sodium and potassium salts. These salts can be prepared according to known methods which are familiar to any person skilled in the art.

The various compounds which are used as starting materials are known or can be prepared according to known methods. The Examples which follow contain detailed information concerning the preparation of the starting materials.

As mentioned earlier, the compounds of formula Ia inhibit the enzyme COMT. This activity can be determined quantitatively as follows: Rat liver homogenate is incubated in the presence of a suitable substrate as described in J. Neurochem. 38, 191–195 (1982) and the COMT activity is measured. In a second series of experiments the incubation is carried out in the presence of a compound of formula Ia. The IC_{50} can then be calculated from the difference of the COMT activity which is determined. IC_{50} is given in nmol/l and is that concentration in the incubation mixture which is required to reduce the COMT activity by 50%. The IC_{50} values for some compounds of formula Ia are given in the following Table. Moreover, this Table contains data concerning the acute toxicity of these compounds (LD_{50} in mg/kg in the case of single oral administration to mice).

Compound of formula Ia	IC_{50} in nmol/l	LD_{50} in mg/kg p.o.
3,4-Dihydroxy-5-nitrophenyl 2-pyridyl ketone	53.4	1250
3,4-Dihydroxy-5-nitrophenyl 3-pyridyl ketone	47.0	1000

-continued

Compound of formula Ia	IC_{50} in nmol/l	LD_{50} in mg/kg p.o.
3,4-Dihydroxy-5-nitrophenyl 4-pyridyl ketone	67.0	1000–2000
n-Butyl 3,4-dihydroxy-5--nitrobenzoate	20.0	312–625
n-Butyl 3,4-dihydroxy-5--nitrocinnamate	25.9	2500–5000
Ethyl 3,4-dihydroxy-5--nitrophenylglyoxylate	48.1	1250–2500
3,4-Dihydroxy-5-nitrobenzophenone	48.0	500–1000
3,5-Dinitropyrocatechol	36.9	500–1000
2'-Fluoro-3,4-dihydroxy-5-nitrobenzophenone	42.0	312–625

The compounds of formula Ia, ester or ether derivatives thereof, and salts thereof can be used as medicaments, for example, in the form of pharmaceutical preparations for enteral or parenteral administration. The compounds of formula Ia can be administered, for example, perorally, for example in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, for example, in the form of suppositories, or parenterally, for example, in the form of injection solutions.

The manufacture of the pharmaceutical preparations can be effected in a manner which is familiar to any person skilled in the art by bringing the compounds of formula Ia, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, the usual pharmaceutical adjuvants.

As carrier materials there are suitable not only inorganic carrier materials, but also organic carrier materials. Thus, for tablets, coated tablets, dragees and hard gelatine capsules there can be used as carrier materials, for example, lactose, maize starch or derivatives thereof, talc, stearic acid or its salts. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols. Depending on the nature of the active substances no carriers are, however, required in the case of soft gelatine capsules. Suitable carrier materials for the preparation of solutions and syrups are, for example, water, polyols, saccharose, invert sugar and glucose. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerine and vegetable oils. Suitable carrier materials for suppositories are, for example natural or hardened oils, waxes, fats and semi-liquid or liquid polyols.

As pharmaceutical adjuvants there come into consideration the usual preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, flavor-improving agents such as sweetening agents and flavoring agents, coloring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants.

The dosage of the compounds of formula Ia, ester or ether derivatives thereof and salts thereof can vary within wide limits depending on the illness to be treated, the age and the individual condition of the patient and on the mode of administration and will, of course, be fitted to the individual requirements in each particular case. In the improvement of the treatment of Parkinson's disease and of parkinsonism with L-dopa a daily dosage of 25 mg to about 1000 mg, especially about 100 mg to about 300 mg, comes into consideration. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations in accordance with the invention conveniently contain about 25 mg to about 300 mg, preferably about 50 mg to about 150 mg, of a compound of formula Ia or of an ester or ether derivative thereof which is hydrolyzable under physiological conditions or of a pharmaceutically acceptable salt thereof.

The Examples which follow further illustrate the invention. All temperatures are given in degrees Celsius.

EXAMPLE 1

a) 17.1 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde are treated with 170 ml of constant-boiling hydrobromic acid and heated under reflux for 3.5 hours. After cooling the separated precipitate is filtered under suction, washed twice with ice-water and taken up in ethyl acetate. The organic phase is washed twice with 50 ml of sodium chloride solution each time, dried over magnesium sulfate and evaporated in a water-jet vacuum. The crystals obtained are taken up in methylene chloride, whereupon the solution is filtered over a ten-fold amount of silica gel. The material obtained is crystallized from ethyl acetate/isopropyl ether. There is obtained 3,4-dihydroxy-5-nitrobenzaldehyde in the form of yellow crystals of m.p. 142°–143°.

b) a solution of 1.7 g of hydroxylamine O-sulfonic acid in 6 ml of water is added to a solution of 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde in 25 ml of water, subsequently stirred at 65° for 3.5 hours, cooled, the separated precipitate is filtered off under suction and taken up in ethyl acetate. The organic phase is dried over sodium sulfate and evaporated in a water-jet vacuum. The crystals obtained are recrystallized from ethyl acetate/n-hexane. There is obtained 3,4-dihydroxy-5-nitrobenzonitrile in the form of yellow crystals of m.p. 194°–195°.

EXAMPLE 2

aa) 10 ml of tert.butyl lithium solution (1.4M in hexane) are added dropwise at −70° within 10 minutes to 4.1 g of 4-(benzyloxy)-3-methoxy-bromobenzene dissolved in 40 ml of tetrahydrofuran. After stirring at −70° for 2 hours. 1 ml of pyridine-3-carbaldehyde is added within 5 minutes The reaction mixture is stirred at −70° for 1 hour and at 0° for 2 hours. and poured into 100 ml of 1N hydrochloric acid. The mixture is extracted three times with 50 ml of ether each time. The combined ether phases are washed with 100 ml of 1N hydrochloric acid and 20 nl of water. The combined aqueous phases are made alkaline with aqueous ammonia solution and extracted three times with 100 ml of methylene chloride each time. The combined methylene chloride phases are dried over sodium sulfate and evaporated. There is obtained alpha-[4-(benzyloxy)-3-methoxyphenyl]-3-pyridinemethanol as an oil.

ab) In an analogous manner, using pyridine-4-carbaldehyde there is obtained alpha-[4-(benzyloxy)-3-methoxyphenyl]-4-pyridinemethanol as an oil.

ba) 3.2 g of alpha-[4-(benzyloxy)-5-methoxyphenyl]-3-pyridinemethanol suspended in 50 ml of water are treated with 2.5 g of potassium permananate, whereupon the mixture is stirred at 90° for 30 minutes After adding a further 1.0 g of potassium permanganate and stirring for a further 30 minutes at 90° the mixture is cooled to room temperature and extracted twice with

150 ml of ethyl acetate each time. The combined ethyl acetate phases are washed with sodium chloride solution, dried over sodium sulfate and evaporated. The thus-obtained residue is chromatographed on 50 g of silica gel with ethyl acetate. After recrystallization from methylene chloride/hexane there is obtained 4-(benzyloxy)-3-methoxyphenyl 3-pyridyl ketone of m.p. 76°.

bb) In an analogous manner, from alpha-[4-(benzyloxy)-3-methoxyphenyl)-4-pyridinemethanol there is obtained 4-(benzyloxy)-3-methoxyphenyl 4-pyridyl ketone of m.p. 85°-87° (methylene chloride/hexane).

ca) 50 ml of 33 percent hydrobromic acid in acetic acid are added dropwise within 15 minutes at 10° to 20 g of 4-(benzyloxy)-3-methoxyphenyl 3-pyridyl ketone dissolved in 200 ml of methylene chloride. After stirring at 20° for 3 hours, the reaction mixture is poured into a mixture of 100 ml of conc. aqueous ammonia and ice. The pH is adjusted to 6 by adding acetic acid. The methylene chloride phase is separated; the aqueous phase is extracted twice more with 100 ml of methylene chloride each time. The combined methylene chloride phases are dried over sodium sulfate and evaporated. The residue is recrystallized from methylene chloride/-hexane. There is obtained 4-hydroxy-3-methoxyphenyl 3-pyridyl ketone of m.p. 150°-151°.

cb) In an analogous manner, from 4-(benzyloxy)-3-methoxyphenyl 4-pyridyl ketone there is obtained 4-hydroxy-3-methoxyphenyl 4-pyridyl ketone of m.p. 215°-218° (acetonitrile).

da) 0.38 ml of 65 percent nitric acid is added dropwise at room temperature to 1.15 g of 4-hydroxy-3-methoxyphenyl 3-pyridyl ketone dissolved in 15 ml of acetic acid. After stirring for 2 hours, the reaction mixture is poured into 120 ml of ice-water, whereupon the mixture is adjusted to pH 5 with conc. ammonia and the precipitate formed is filtered off. The thus-obtained residue is heated under reflux in 20 ml of acetonitrile, whereupon it is again filtered off. There is obtained 4-hydroxy-3-methoxy-5-nitrophenyl 3-pyridyl ketone as brown crystals of m.p. 193°.

db) In an analogous manner, from 4-hydroxy-3-methoxyphenyl 4-pyridyl ketone there is obtained 4-hydroxy-3-methoxy-5-nitrophenyl 4-pyridyl ketone of m.p. 240°.

e) 3.5 g of 4-hydroxy-3-methoxy-5-nitrophenyl 3-pyridyl ketone dissolved in 70 ml of 48 percent aqueous hydrobromic acid are stirred at 100° for 18 hours. The reaction mixture is subsequently evaporated under reduced pressure. The residue is recrystallized from water. There is obtained 3,4-dihydroxy-5-nitrophenyl 3-pyridyl ketone hydrobromide of m.p. 265°.

f) In an analogous manner, from 4-hydroxy-3-methoxy-5-nitrophenyl 4-pyridyl ketone there is obtained 3,4-dihydroxy-5-nitrophenyl 4-pyridyl ketone of m.p. 246° (from water).

g) 13.2 g of 3,4-dihydroxy-5-nitrophenyl 4-pyridyl ketone are suspended in 500 ml of methanol and treated while stirring with 4.88 g of methanesulfonic acid. The suspension is heated under reflux for 60 minutes. It is subsequently cooled to 10°, the crystals are filtered under suction and washed twice with 30 ml of methanol each time. There is obtained 3,4-dihydroxy-5-nitrophenyl 4-pyridyl ketone methanesulfonate of m.p. 260°-261° (dec.).

EXAMPLE 3

a) A solution of 2.6 g of 4-hydroxy-3-methoxy-5-nitrobenzoic acid in 26 ml of constant-boiling hydrobromic acid is heated under reflux for 2 hours. After cooling the solvent is distilled in a water-jet vacuum. The crystalline residue is recrystallized from 50 ml of water at boiling temperature. There is obtained 3,4-dihydroxy-5-nitrobenzoic acid in the form of yellow crystals of m.p. 224°-226°.

b) 1.0 g of 3,4-dihydroxy-5-nitrobenzoic acid is treated with 20 ml of methanolic hydrochloric acid, stirred at 45° for 3 hours and, after removing the solvent, the residue is taken up in methylene chloride. The organic phase is washed with sodium chloride solution, dried over sodium sulfate and evaporated. The crystalline product obtained is taken up in methylene chloride and filtered over a ten-fold amount of silica gel. The material obtained is recrystallized from ethyl acetate/n-hexane. There is obtained methyl 3,4-dihydroxy-5-nitrobenzoate in the form of yellow crystals of m.p. 144°-145°.

The following esters are obtained in an analogous manner starting from 3,4-dihyroxy-5-nitrobenzoic acid:

c) Ethyl 3,4-dihydroxy-5-nitrobenzoate of m.p. 106°-107° (from ethyl acetate/n-hexane),

d) n-butyl 3,4-dihydroxy-5-nitrobenzoate of m.p. 73°-74° (from methylene chloride) and

e) n-hexyl 3,4-dihyroxy-5-nitrobenzoate of m.p. 44°-45° (from isopropyl ether).

EXAMPLE 4

a) 25 ml of 2M phenyl lithium solution (in benzene/ether (7:3)) are added dropwise within 15 minutes to 10.0 g of 3,4-dimethoxy-5-nitrobenzaldehyde dissolved in 150 ml of tetrahydrofuran and the mixture stirred at 0° for 1 hour and at 20° for 2 hours. The mixture is subsequently treated with 150 ml of 2N sulfuric acid and extracted three times with 150 ml of ether. The combined ether phases are washed with sodium chloride solution, dried over sodium sulfate and evaporated. The thus-obtained residue is chromato graphed on 180 g of silica gel with methylene chloride. There is obtained 3,4-dimethoxy-5-nitrobenzhydrol as an amorphous solid.

b) 2.5 g of 3,4-dimethoxy-5-nitrobenzhydrol dissolved in 50 ml of methylene chloride are treated with 2.2 g of pyridinium chlorochromate, whereupon the mixture is stirred at room temperature for 2hours. The insoluble constituents are subsequently filtered. The filtrate is evaporated and the residue is chromatographed on 60 g of silica gel with ethylene chloride. After crystallization from methylene chloride/hexane there is obtained 3,4-dimethoxy-5-nitrobenzophenone of m.p. 78°-80°.

c) 0.5 g of 3,4-dimethoxy-5-nitrobenzophenone is stirred at 100° for 30 hours in a mixture of 4 ml of acetic acid and 4 ml of 48 percent aqueous hydrobromic acid. The reaction mixture is subsequently evaporated to dryness. The residue is taken up in methylene chloride. It is washed with water, dried over sodium sulfate and evaporated. After recrystallization from methylene chloride/hexane there is obtained 3,4-dihydroxy-5-nitrobenzophenone of m.p. 132°.

EXAMPLE 5

a) 4.9 g of magnesium are suspended in 15 ml of absolute ethanol and, after adding 1 ml of carbon tetra-chloride, warmed until the reaction starts. A solution of 31.8 g of diethyl malonate in 19.9 ml of absolute ethanol and 80 ml of absolute toluene is then added dropwise while stirring so that the temperature lies between 50° and 60°

The reaction mixture is subsequently stirred at this temperature for an additional 1 hour, whereupon it is cooled to −5° and a solution of 49.3 g of 3,4-dimethoxy-5-nitrobenzoyl chloride (m.p. 82°–85°) in 300 ml of absolute toluene and 50 ml of absolute tetrahydrofuran is added dropwise so that the temperature does not exceed −5°. The mixture is subsequently stirred at room temperature overnight. After distillation of the solvent the residue is dissolved in 500 ml of ethyl acetate. The solution is treated while stirring and cooling with ice with an ice-cold solution of 12 ml of concentrated sulfuric acid in 80 ml of water. The organic phase is washed with sodium chloride solution, dried over magnesium sulfate and evaporated. The oil obtained is chromatographed on a ten-fold amount of silica gel with methylene chloride. The crystalline material obtained is recrystallized from isopropyl ether. There is obtained diethyl 3,4-dimethoxy-5-nitrobenzoylmalonate in the form of pale beige crystals of m.p. 70°.

b) 19.0 g of diethyl 3,4-dimethoxy-5-nitrobenzoylmalonate are dissolved in 100 ml of glacial acetic acid, 5 drops of concentrated sulfuric acid are added thereto and the mixture is heated under reflux for 16 hours. The acetic acid is distilled at 60° in a water-jet vacuum and the residue is treated three times with 250 ml of toluene each time, whereby it is evaporated each time. The crystalline residue is extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate and evaporated. The crystals obtained are chromatographed on a 30-fold amount of silica gel with toluene. The crystalline material obtained is recrystallized from isopropyl ether. There is obtained 3,4-dimethoxy-5'-nitroacetophenone in the form of yellowish crystals of m.p. 86°–87°.

c) 2 g of 3',4'-dimethoxy-5'-nitroacetophenone are treated with 30 ml of constant-boiling hydrobromic acid and stirred at 140° for 2.5 hours. After cooling the mixture is poured into 200 ml of ice-water and extracted three times with 100 ml of ethyl acetate each time. The organic phase is washed twice with 25 ml of sodium chloride solution each time, dried over sodium sulfate and evaporated. The product obtained is filtered with ethyl acetate over a 20-fold amount of silica gel. By recrystallization of the material obtained from water there is obtained 3',4'-dihydroxy-5'-nitroacetophenone in the form of yellow crystals of m.p. 159°–160°.

The same compound is obtained starting from 4'-hydroxy-3'-methoxy-5'-nitroacetophenone by treatment with hydrobromic acid at the boiling temperature.

EXAMPLE 6

a) 100 g of guaiacol are dissolved in 136.4 g of isobutyric anhydride, treated with 120 g of anhydrous zinc chloride (whereby all passes into solution), the reaction mixture is heated to 155° and cooled after three minutes. The residue is first subjected to a steam distillation in order to remove readily volatile constituents and is then extracted three times with 500 ml of ether each time. The organic phase is washed twice with 250 ml of water each time, once with 150 ml of saturated bicarbonate solution and again with 250 ml of water, dried over sodium sulfate and evaporated in a water-jet vacuum. The brown resin obtained is distilled in a high vacuum. The distillate of b.p. 105°–120° (6.67 Pa) is dissolved in ether, whereupon the solution is treated with n-hexane until crystallization begins. The crystals obtained are recrystallized from ether/hexane. There is obtained 4'-hydroxy-3'-methoxy-2-methyl-propiophenone in the form of colorless crystals of m.p. 86°–87°.

b) 15.0 g of 4'-hydroxy-3'-methoxy-2-methyl-propiophenone are dissolved in 300 ml of glacial acetic acid and 7.65 ml of 50.5 percent nitric acid (11.2N) in 40 ml of glacial acetic acid are added dropwise thereto while stiring within 15 minutes. After 15 minutes the reaction mixture is poured into ice-water and the separated crystals are filtered under suction, washed with water and dissolved in methylene chloride. The solution is dried over sodium sulfate and evaporated. The crude product obtained is taken up on methylene chloride and filtered over 100 g of silica gel. The thus-obtained crystals are recrystallized from methylene chloride/n-hexane. There is obtained 4'-hydroxy-3'-methoxy-2-methyl-5'-nitropropiophenone in the form of yellow crystals of m.p. 85°–87°.

c) 8.0 g of 4'-hydroxy-3'-methoxy-2-methyl-5'-nitropropiophenone are treated with 64 g of pyridine hydrochloride and stirred at 180° for 45 minutes. After cooling the reaction mixture is poured into 500 ml of ice-water, whereupon it is made acid with 20 ml of 3N hydrochloric acid and extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulfate and evaporated in a water-jet vacuum. After crystallization from methylene chloride/n-hexane there is obtained 3',4'-dihydroxy-2-methyl-5'-nitropropiophenone in the form of yellow crystals of m.p. 98°–99°.

EXAMPLE 7

a) 100 g of guaiacol are dissolved in 136.4 g of butyric anhydride, treated with 120 g of zinc chloride, heated for 3 minutes as given in Example 6.a and then worked-up as described there. The crude product obtained after high vacuum distillation is chromatographed with toluene on 600 g of silica gel. After recrystallization from ether/n-hexane there is obtained 4'-hydroxy-3'-methoxy-butyrophenone in the form of colorless crystals of m.p. 40°–41°.

b) 6.5 ml of 11.2N nitric acid are added dropwise to a solution of 12.7 g of 4'-hydroxy-3'-methoxybutyrophenone in 250 ml of glacial acetic acid while stirring within 10 minutes. The reaction mixture is subsequently stirred for 15 minutes, poured into ice-water, the separated precipitate is filtered under suction, washed with ice-water and taken up in methylene chloride. The methylene chloride solution is filtered over 50 g of silica gel. The material obtained is recrystallized from methylene chloride/n-hexane. There is obtained 4'-hydroxy-3'-methoxy-5'-nitrobutyrophenone in the form of yellow crystals of m.p. 92°–93°.

c) 10.2 g of 4'-hydroxy-3'-methoxy-5'-nitrobutyrophenone are treated with 80 g of pyridine hydrochloride and stirred at 200° for 40 minutes. After cooling the reaction mixture is poured into 500 ml of ice-water. The mixture is treated with 30 ml of 3N hydrochloric acid and extracted with methylene chloride. The organic phase is dried over sodium sulfate and evaporated. The crude product obtained is chromatographed with methylene chloride on 150 g of silica gel. The material obtained is recrystallized from methylene chloride/n-hexane. There is obtained 3',4'-dihydroxy-5'-nitrobutyrophenone in the form of yellow crystals of m.p. 88°–90°.

EXAMPLE 8

a) 2.25 g of 3,4-dihydroxy-5-nitrocinnamic acid are dissolved in 50 ml of methanol and hydrochloric acid gas is introduced into this solution for 10 minutes. After 1 hour 50 ml of isopropyl ether are added thereto, and the separated precipitate is filtered under suction and washed with isopropyl ether. After recrystallization from methanol/ether there is obtained methyl 3,4-dihydroxy-5-nitrocinnamate in the form of yellow crystals of m.p. 186°-187°.

b) In an analogous manner, from 3,4-dihydroxy-5-nitrocinnamic acid and butanolic hydrochloric acid solution there is obtained n-butyl 3,4-dihydroxy-5-nitrocinnamate in the form of yellowish crystals of m.p. 129°-130°.

EXAMPLE 9

5.0 g of diethyl 3,4-dimethoxy-5-nitrobenzoyl malonate are dissolved in 50 ml of absolute methylene chloride. After cooling to −20° a solution of 16.9 g of boron tribromide in 30 ml of methylene chloride is added dropwise thereto while stirring so that the temperature does not exceed −20°. The mixture is subsequently stirred at room temperature overnight. After adding 80 ml of ethanol the mixture is stirred at room temperature for 30 minutes and the solvent is subsequently distilled in a water-jet vacuum. The residue is treated with water and extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulfate and evaporated. The crude product obtained is filtered with ethyl acetate over 50 g of silica gel. The crystalline residue obtained is recrystallized from methylene chloride/n-hexane. There is obtained ethyl 3,4-dihydroxy-5-nitro-benzoylacetate in the form of yellow crystals of m.p. 141°-142°.

EXAMPLE 10

a) A solution of 1.49 g of 2-phenylethylamine in 100 ml of methylene chloride is treated with 1.26 g of triethylamine. A solution of 3.0 g of 3,4-dimethoxy-5-nitrobenzoyl chloride in 100 ml of methylene chloride is added dropwise thereto while stirring, whereupon the mixture is stirred for a further 15 minutes. The organic phase is then extracted twice with 50 ml of ice-water each time, dried over sodium sulfate and evaporated in a water-jet vacuum. After recrystallization from methylene chloride/n-hexane there is obtained 3,4-dimethoxy-5-nitro-N-phenethylbenzamide in the form of pale beige needles of m.p. 121°-122°.

b) 3.6 g of 3,4-dimethoxy-5-nitro-N-phenylbenzamide are heated under reflux with 35 ml of phosphorus oxychloride under a nitrogen atmosphere for 96 hours. After distilling the excess phosphorus oxychloride in a water-jet vacuum at 60°, the residue is treated three times with 100 ml of toluene each time, with the solvent being distilled each time. The residue is taken up in methylene chloride. The organic phase is washed with water, dried over sodium sulfate and evaporated in a water-jet vacuum. The red resin obtained is chromatographed on 120 g of silica gel with methylene chloride/ethyl acetate (1:1). There is obtained 1-(3,4-dimethoxy-5-nitrophenyl)-3,4-dihydroisoquinoline in the form of a yellow resin.

c) 1.4 g of 1-(3,4-dimethoxy-5-nitrophenyl)-3,4-dihydroisoquinoline are treated with 15 ml of constant-boiling hydrobromic acid and heated to boiling under reflux under a nitrogen atmosphere for 1.5 hours. After distilling the hydrobromic acid in a water-jet vacuum, the crystalline residue is recrystallized from acetone. There is obtained 5-(3,4-dihydro-1-isoquinolinyl)-3-nitropyrocatechol hydrobromide in the form of yellow crystals of m.p. >250° (decomposition).

EXAMPLE 11

a) 5.0 g of 4-hydroxy-5-methoxy-isophthalaldehyde are treated with 50 ml of constant-boiling hydrobromic acid and heated to boiling under reflux and while stirring under an argon atmosphere for 3 hours. After cooling 50 ml of ice-water are added thereto, and the separated precipitate is filtered under suction and washed with water. The crude product is taken up in ethyl acetate and filtered over 50 g of aluminum oxide (activity grade II). The crystalline material obtained is recrystallized from ethyl acetate/n-hexane. There is obtained 4,5-dihydroxyisophthalaldehyde in the form of slightly orange crystals of m.p. 201°-202°.

b) A solution of 3.27 g of hydroxylamine O-sulfonic acid in 12 ml of water is added dropwise at 30° while stirring to a solution of 2.0 g of 4,5-dihydroxyisophthalaldehyde in 20 ml of water, whereupon the mixture is held at 65° for 10 hours. After cooling the separated precipitate is filtered under suction, washed with water and taken up in ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and evaporated in a water-jet vacuum. After recrystallization from ethyl acetate there is obtained 4,5-dihydroxyisophthalonitrile in the form of yellow crystals which decompose above 300°.

EXAMPLE 12

a) A solution of 38 g of fuming nitric acid (96%) in 50 ml of glacial acetic acid is added dropwise while stirring and within 30 minutes at 20°-25° to a solution of 112.5 g of 2-bromo-4'-hydroxy-3'-methoxyacetophenone in 560 ml of glacial acetic acid. Yellow-brown crystals thereby separate. After 90 minutes the reaction mixture is poured on to 300 g of ice. The crystals are filtered under suction, washed with 1000 ml of water and dissolved in 1000 ml of methylene chloride. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and the filtrate is evaporated at 50° in a water-jet vacuum until crystallization begins. The crystallizate, cooled to room temperature, is removed by filtration under suction and washed with a small amount of methylene chloride. There is obtained 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone of m.p. 147°-149°.

b) Method A:

ba) A suspension of 580.1 mg of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone in 10 ml of ethanol is treated with 443.8 mg of selenium dioxide and heated under reflux for 71 hours. Thereafter, the selenium is removed by filtration and the filtrate is evaporated. The residue is dissolved in methylene chloride, washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. There is obtained ethyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p 165°-167° (from ethanol).

In an analogous manner:

bb) From 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and n-butanol there is obtained n-butyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p. 105°-107° (from ethanol) and

bc) from 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and n-hexanol there is obtained

hexyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p. 103°–105° (from n-hexanol/petroleum ether).

c) Method B:

ca) A suspension of 29.01 g of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone in 300 ml of tert.butanol is treated with 27.74 g of selenium dioxide and heated to boiling under reflux for 18 hours. The hot reaction mixture is suction filtered through a filter aid of diatomaceous earth while rinsing with methylene chloride. The filtrate is evaporated and the residue is suspended in 150 ml of hot methylene chloride. The crystalline precipitate is filtered under suction and washed with a small amount of methylene chloride. There is obtained 4-hydroxy-3-methoxy-5-nitrophenylglyoxylic acid of m.p. 169°–171°.

2.42 g of 4-hydroxy-3-methoxy-5-nitrophenylglyoxylic acid are dissolved in 25 ml of dry N,N-dimethylformamide, treated at room temperature with 50 mg of 4-dimethylaminopyridine and 920 mg of dry methanol, subsequently cooled to 0° with an ice-bath and 2.27 g of N,N-dicyclohexylcarbodiimide are added thereto. After 10 minutes the ice-bath is removed and the reaction mixture is stirred for a further 1 hour at room temperature. The mixture is subsequently evaporated. The residue is dissolved in ethyl acetate, whereupon insoluble urea is filtered, the filtrate is washed four times with water, dried over sodium sulfate, filtered and evaporated. There is obtained methyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p. 155°–157° (from methylene chloride/ether).

In an analogous manner:

cb) From 4-hydroxy-3-methoxy-5-nitrophenylglyoxylic acid and ethanol there is obtained ethyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p. 165°–167° (from ethanol) and

cc) From 4-hydroxy-3-methoxy-5-nitrophenylglyoxylic acid and isopropanol there is obtained i-propyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate of m.p. 99°–101° (from isopropanol).

d) A suspension of 17.2 g of ethyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate in 100 of dry acetonitrile and 100 ml of dry toluene is treated with 10.53 g of sodium iodide and 11.9 g of silicon tetrachloride and heated under reflux for 47 hours. The reaction mixture is then evaporated and the residue is distilled six times with 200 ml of toluene each time. The residue obtained is partitioned between water and ether and filtered through a filter aid of diatomaceous earth. The ethereal phase is washed four times with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The oily residue is treated three times with ether and active carbon. There is obtained ethyl 3,4-dihydroxy-5-nitrophenylglyoxylate of m.p. 77°–79° (from ether/n-hexane).

In an analogous manner:

e) From methyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate there is obtained methyl 3,4-dihydroxy-5-nitrophenylglyoxylate as a yellow distillate at 145°–150° and 10.67 Pa.

f) from isopropyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate there is obtained isopropyl 3,4-dihydroxy-5-nitrophenylglyoxylate as a yellow distillate at 155°–160° and 12.0 Pa,

g) from n-butyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate there is obtained n-butyl, 3,4-dihydroxy-5-nitrophenylglyoxylate as a yellow distillate at 160°–165° and 10.67 Pa and

h) from n-hexyl 4-hydroxy-3-methoxy-5-nitrophenylglyoxylate there is obtained hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate as a yellow distillate at 165°–170° and 12.0 Pa.

EXAMPLE 13

236.1 mg of n-hexyl 3,4-dihydroxy-nitrophenylglyoxylate are dissolved in 15 ml of ethanol and treated with 7.59 ml of 0.1N sodium hydroxide solution. After 1 hour the reddish-yellow solution is evaporated. The resulting sodium salt of the n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate is crystallized from water and has a m.p. of ~300°.

EXAMPLE 14

A solution of 3.18 g of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate in 47.5 ml of ethanol is treated with 1.11 g of O-methylhydroxylamine hydrochloride, 1.95 g of sodium acetate and 2.5 ml of water and heated to boiling under reflux for 5 hours. Thereafter, the reaction mixture is evaporated and the residue is treated with ether and water. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue is chromatographed on silica gel with methylene chloride. There is obtained a 7:3 mixture of n-hexyl E- and Z-3,4-dihydroxy-5-nitrophenylglyoxylate O-methyl oxime as a reddish oil: 80 MHz NMR spectrum ($CDCl_3$): signal for O-methyl at 3.96 and 4.05 ppm.

EXAMPLE 15

A solution of 5.1 g of ethyl 3,4-dihydroxy-5-nitrophenylglyoxylate in dry methylene chloride is treated dropwise at −10° within 15 minutes with 25 g of boron tribromide. The mixture is then stirred at −10° for 1 hour and subsequently at room temperature for 17 hours. Thereafter, the reaction mixture is evaporated, the residue is treated cautiously with water and stirred at 50° for an additional 30 minutes. After cooling to room temperature, the flocculent precipitate is filtered under suction. The aqueous phase is acidified with 10 ml of 1N hydrochloric acid, extracted four times with ether, the combined organic extracts are washed four times with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The crude product is filtered three times in succession in ether through a filter aid of diatomaceous earth. There is obtained 3,4-dihydroxy-5-nitrophenylglyoxylic acid of m.p. 172°–174° from isopropyl ether).

EXAMPLE 16

a) a mixture of 3.93 g of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 1.38 g of 2-aminophenol is melted at 120° while stirring. The melt crystallizes after 5 minutes. After 2 hours it is cooled and recrystallized from methanol. There is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one of m.p. 202°–204°.

In an analogous manner:

b) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 2-amino-p-cresol there is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one of m.p. 233°–235° (from methanol/methylene chloride).

c) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 2-amino-4-propylphenol there is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-6-propyl-2H-1,4-benzoxazin-2-one of m.p. 200°–202° (from methanol)

d) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 3-amino-4-hydroxybenzoic acid there is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-2-oxo-2H-1,4-benzoxazine-6-carboxylic acid of m.p. 286°-287° (from acetone/petroleum ether).

e) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 2-amino-4-chlorphenol there is obtained 6-chloro-3-(3,4-dihydroxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one of m.p. 241°-243° (from methanol).

f) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 2-amino-4,6-dichlorophenol there is obtained 6,8-dichloro-3(3,4-dihydroxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one or m.p. 237°-239° (from ethanol/ether) and

g) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 2-amino-5-nitrophenol there is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-7-nitro-2H-1,4-benzoxazin-2-one of m.p. 253°-255° (from acetonitrile/ethanol).

EXAMPLE 17

a) A mixture of 396.0 mg of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 137.6 mg of 1,2-phenylenediamine is heated to 120° for 60 minutes. Thereafter, the mixture is suspended in methanol, filtered under suction and recrystallized from N,N-dimethylformamide/water. There is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone of m.p. >300 °.

In an analogous manner:

b) From n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and N-methyl-1,2-phenylene diamine there is obtained 1-methyl-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone of m.p. 271°-273° (from methanol).

c) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and N-propyl-1,2-phenylene diamine there is obtained 1-propyl-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)quinoxalinone of m.p. 183°-185° (from methanol).

d) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 4,5-dimethyl-1,2-phenylenediamine there is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-6,7-dimethyl-2(1H)-quinoxalinone of m.p. >300° (from N,N-dimethylformamide/water).

e) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 4,5-dichloro-1,2-phenylenediamine there is obtained 6,7-dichloro-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone of m.p. >300° (from N,N-dimethylformamide/water),

f) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 3-chloro-5-trifluoromethyl-1,2-phenylenediamine there is obtained a 1:1 mixture of 8(and 5)-chloro-3-(3,4-dihydroxy-5-nitrophenyl)-6 (and 7)-trifluoromethyl-2(1H)-quinoxalinone of m.p. >300° (from N,N-dimethylformamide/water),

g) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 4-methoxy-1,2-phenylenediamine there is obtained a 1:1 mixture of 3-(3,4-dihydroxy-5-nitrophenyl)-6(and 7)-methoxy-2(1H)-quinoxalinone of m.p. >300° (from ethanol/ether),

h) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 4-nitro-1,2-phenylenediamine there is obtained 1:1 mixture of 3-(3,4-dihydroxy-5-nitrophenyl)-6(and 7)-nitro-2(1H)-quinoxalinone of m.p. >300° (from N,N-dimethylformamide/water) and

i) from n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and N-hexyl-1,2-phenylenediamine there is obtained 1-hexyl-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinolalinone of m.p. 152°-154° (from methanol).

EXAMPLE 18

A solution of 1.07 g of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 696.3 mg of 2,3-diaminonaphthalene in 3 ml of 1-hexanol is heated to boiling under reflux for 3 hours. The reaction mixture is then cooled and diluted with methanol. The crude product is filtered under suction and recrystallized from N,N-dimethylformamide/water. There is obtained 3-(3,4-dihydroxy-5-nitrophenyl)-benzo[g]quinoxalin-2(1H)-one of m.p. >300°.

EXAMPLE 19

A suspension of 2.05 g of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 600.8 mg of thiosemicarbazide is stirred intensively at 90° for 30 minutes. The mixture is then cooled to 40° and treated with a solution of 870.1 mg of sodium hydroxide in 15 ml of water. The solution is subsequently heated to 90° for 30 minutes, cooled to room temperature and treated dropwise with 2 ml of conc. hydrochloric acid. The crystallized-out product is filtered under suction and then dissolved in ethyl acetate. The solution is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. There is obtained 6-(3,4-dihydroxy-5-nitrophenyl)-3-mercapto-1,2,4-triazin-5(4H)-one of m.p. 282°-284° (from ethanol).

EXAMPLE 20

aaa) A suspension of 2.9 g of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and 761.2 mg of thiourea in 170 ml of ethanol is treated at 60° with 820.3 mg of sodium acetate and stirred for 6 hours. The reaction mixture is then evaporated, the residue is treated with 170 ml of water and heated to 60° for 30 minutes. After cooling the product is filtered under suction and washed with water. There is obtained 4-(2-amino-4-thiazolyl)-2-methoxy-6-nitrophenol of m.p. 248°-250° (from ethanol).

In an analogous manner:

aab) From 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and N-phenylthiourea there is obtained 4-(2-anilino-4-thiazolyl)-2-methoxy-6-nitrophenol of m.p. 185°-187° (from ether).

aba) 50 ml of 1,2-dichloroethane and 3.56 g of calcium carbonate are added to a solution of 4.88 g of 6-amino-4'-(trifluoromethyl)-hexanilide hydrochloride in 70 ml of water. The suspension is treated within 60 minutes while stirring at room temperature with a solution of 2.6 g of thiophosgene in 1.7 ml of toluene. After 16 hours the precipitate is removed by filtration under suction and the organic phase is washed with 1N hydrochloric acid and water. After drying over sodium sulfate and filtration the filtrate is evaporated. There is obtained crude 4'-(trifluoromethyl)hexananilide-6-isothiocyanate.

abb) A solution of 5.2 g of crude 4'-(trifluoromethyl)-hexananilide-6-isothiocyanate in 60 ml of ethanol is treated with 100 ml of conc. ammonia solution. After 30 minutes the reaction mixture is evaporated. The residue is dissolved in ethyl acetate, washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 1-[5-[(α,α,α-trifluoro-p-tolyl)carbamoyl]-pentyl]-2-thiourea of m.p. 140°-142° (from ethanol).

abc) A suspension of 666.7 mg of 1-[5-[αα,α-trifluoro-p-tolyl)carbamoyl]pentyl]-2-thiourea and 580.2 mg of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone in 50 ml of ethanol is treated at 60° with 164.2 mg of

sodium acetate. A reddish-yellow solution thereby results. After 90 minutes the reaction mixture is evaporated, the residue is treated with water, the precipitate is filtered under suction and washed four times with 10 ml of water each time. There is obtained 6-[[4-hydroxy-3-methoxy-5-nitrophenyl)-2-thiazolyl)]-amino]-4'-(trifluoromethyl)hexananilide of m.p. 160°-162° (from ethanol).

ac) A solution of 29.0 g of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and 13.5 g of 2-aminoacetophenone in 250 ml of dry N,N-dimethylformamide is stirred at 90° for 16 hours. The reaction mixture is then evaporated to about two thirds and poured on to ice. The separated crystals are filtered under suction and dissolved in methylene chloride. The solution is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. There is obtained 2-(4-hydroxy-3-methoxy-5-nitrobenzoyl)-3-methylindole of m.p. 195°-197° (from methylene chloride/methanol).

ada) A suspension of 14.5 g of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and 5.41 g of 1,2-phenylenediamine in 350 ml of methanol is treated with 4.92 g of sodium acetate and the mixture is heated to boiling under reflux for 22 hours. The reaction mixture is then evaporated, the residue is dissolved in methylene chloride, this solution is washed four times with water, dried over sodium sulfate, filtered and evaporated. There is obtained 2-(4-hydroxy-3-methoxy-5-nitrophenyl)quinoxaline of m.p. 195°-197° (from methylene chloride/methanol).

In an analogous manner:

adb) From 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone and 4,5-dimethyl-1,2-phenylenediamine there is obtained 6,7-dimethyl-2-(4-hydroxy-3-methoxy-5-nitrophenyl)quinoxaline of m.p. 207°-209° (from methylene chloride/methanol).

b) A suspension of 267.3 mg of 4-(2-amino-4-thiazolyl)-2-methoxy-6-nitrophenol in 10 ml of dry methylene chloride is treated at −20° with 1.25 g of boron tribromide. After the addition the mixture is stirred at −20° for a further 1 hour and at room temperature without cooling for 18 hours. The reaction mixture is then evaporated, the residue is treated cautiously with water and stirred at 50° for 30 minutes. After cooling to room temperature the mixture is suction filtered and the crude product is removed by filtration and washed with a small amount of water. There is obtained 5-(2-amino-4-thiazolyl)-3-nitropyrocatechol hydrobromide of m.p. 244°-246° (from methanol).

In an analogous manner:

c) From 4-(2-anilino-4-thiazolyl)-2-methoxy-6-nitrophenol there is obtained 5-(2-anilino-4-thiazolyl)-3-nitropyrocatechol of m.p. 202°-204° (from methanol),

d) from 6-[4-(4-hydroxy-3-methoxy-5-nitrophenyl)-2-thiazolyl)amino]-4'-(trifluoromethyl)hexananilide there is obtained 6-[[4-(3,4-dihydroxy-5-nitrophenyl)-2-thiazolyl]amino]-4'-(trifluoromethyl)hexananilide of m.p. 214°-216° (from methanol).

e) from 2-(4-hydroxy-3-methoxy-5-nitrobenzoyl)-3-methylindole there is obtained 5-bromo-2-(3,4-dihydroxy-5-nitrobenzoyl)-3-methylindole of m.p. 265°-267° (from methanol),

f) from 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-quinoxaline there is obtained 2-(3,4-dihydroxy-5-nitrophenyl)-quinoxaline of m.p. 241°-243° (from methanol) and

g) from 6,7-dimethyl-2-(4-hydroxy-3-methoxy-5-nitrophenyl)quinoxaline there is obtained 6,7-dimethyl-2-(3,4-dihydroxy-5-nitrophenyl)quinoxaline of m.p. 274°-276° (from methanol).

EXAMPLE 21

A mixture of 3.12 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and 849.3 mg of thioacetamide are heated to boiling under reflux for 18 hours in 40 ml of ethanol. After cooling, the crystals are filtered under suction and recrystallized from methanol/isopropanol. There is obtained 5-(2-methyl-4-thiazolyl)-3-nitropyrocatechol hydrobromide of m.p. 280°-282°.

EXAMPLE 22

A solution of 1.38 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and 461 mg of thiosemicarbazide in 20 ml of n-butanol is heated to boiling under reflux for 60 minutes. After cooling to room temperature the crystals are filtered under suction and recrystallized from n-butanol. There is obtained 5-(2-amino-6H-1,3,4-thiadiazin-5-yl)-3-nitropyrocatechol hydrobromide of m.p. 265°-267°.

EXAMPLE 23

A solution of 1.38 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and 505.7 mg of 2-amino-1,3,4-thiadiazole in 25 ml of n-butanol is heated to boiling under reflux for 7 hours. The reaction mixture is then cooled to room temperature and the separated crystals are filtered under suction. There is obtained 5-(imidazo-[2,1-b]-1,3,4-thiadiazol-6-yl)-3-nitropyrocatechol of m.p. 278°-280° (from methanol).

EXAMPLE 24

A mixture of 2.78 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone, 1.01 g of 2-aminothiazole and 40 ml of ethanol is heated to boiling under reflux for 23 hours. The reaction mixture is then cooled to room temperature and the crystals are removed by filtration under suction. There is obtained 5-(imidazo[2,1-b]thiazol-6-yl)-3-nitropyrocatechol hydrobromide of m.p. 286°-288° (from methanol).

EXAMPLE 25

A mixture of 1.95 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone, 1.06 g of 2-aminobenzothiazole and 50 ml of ethanol is heated to boiling under reflux for 17 hours. The reaction mixture is then cooled to room temperature, whereupon the crystals are removed by filtration under suction. There is obtained 5-(imidazo[2,1-b]benzothiazol-2-yl)-3-nitropyrocatechol of m.p. 303°-305° (from N,N-dimethylformamide/methanol).

EXAMPLE 26

A mixture of 2.78 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone, 1.51 g of 2-aminothiophenol and 50 ml of ethanol is heated to boiling under reflux for 1 hour. The reaction mixture is then cooled to room temperature, whereupon the crystals are removed by filtration under suction. There is obtained 5-(2H-1,4-benzothiazin-3-yl)-3-nitropyrocatechol of m.p. 302°-304° (from N,N-dimethylformamide/methanol).

EXAMPLE 27

A mixture of 987.5 mg of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and 1.01 g of 2-aminopyridine is

melted at 110°. After 30 minutes the melt is treated with 15 ml of ethanol and heated to boiling under reflux for 3 hours. The reaction mixture is then cooled to room temperature and the crystals are removed by filtration under suction. There is obtained 5-(imidazo[1,2-a]-pyridin-3-yl)-3-nitropyrocatechol of m.p. 250°-252° (from N,N-dimethylformamide/methanol).

EXAMPLE 28

a) 8.9 g of 1,1'-carbonyldiimidazole are added to a solution of 10.7 g of 4-hydroxy-3-methoxy-5-nitrobenzoic acid in 500 ml of dry tetrahydrofuran and the reaction mixture is subsequently heated to 65°-70° for 5 hours. It is then cooled to room temperature and a solution of 21.6 g of 6-aminohexyl-t-butylcarbamate in 50 ml of dry tetrahydrofuran is added dropwise thereto within 15 minutes. The reaction mixture is then heated to 65°-70° for 18 hours, evaporated, the residue is suspended in ethyl acetate, suction filtered and the suction filtered material is chromatographed on silica gel with acetone-methylene chloride (3:1). There is obtained [6-(4-hydroxy-5-nitro-m-anisamido)hexyl]-t-butylcarbamate of m.p. 145°-147° (from isopropanol).

b) 5.8 ml of hydrobromic acid in glacial acetic acid (~33 percent) are added at room temperature to a solution of 4.1 g of [6-(4-hydroxy-5-nitro-m-anisamido)-hexyl]-t-butylcarbamate in 80 ml of glacial acetic acid. The mixture is stirred for 2 hours, the separated crystals are removed by filtration under suction and washed with ether. There is obtained N-(6-aminohexyl)-4-hydroxy-5-nitro-m-anisamide hydrobromide of m.p. 207°-209° (from isopropanol).

c) 1.25 g of boron tribromide are added −20° to a suspension of 392.3 mg of N-(6-aminohexyl)-4-hydroxy-5-nitroanisamide hydrobromide in 25 ml of dry methylene chloride. After the addition the mixture is stirred at −20° for 1 hour and subsequently at room temperature for 17 hours. The reaction mixture is then evaporated, the residue is treated with 10 ml of water and stirred at room temperature for 1 hour. After evaporating the water the residue is chromatographed on Sephadex LH 20 with toluene/ethanol (1:1). There is obtained N-6-aminohexyl-3,4-dihydroxy-5-nitrobenzamide hydrobromide of m.p. 205°-207° (from ethanol).

EXAMPLE 29

aa) A solution of 4.93 g of 5-nitrovanillin and 2.7 g of 1,2-phenylenediamine in 45 ml of methanol and 15 ml of nitrobenzene is heated to boiling under reflux. After 15 minutes crystals begin to separate from the red solution. After 18 hours the reaction mixture is cooled to room temperature and diluted with 60 ml of methanol. The crystals are filtered under suction and washed with methanol. There is obtained 4-(2-benzimidazolyl)-2-methoxy-6-nitrophenol of m.p. 198°-200° (from N,N-dimethylformamide/methanol).

In an analogous manner:

ab) From 5-nitrovanillin and 4,5-dichloro-1,2-phenylenediamine there is obtained 4-(5,6-dichloro-2-benzimidazolyl)-2-methoxy-6-nitrophenol of m.p. 258°-260° (from N,N-dimethylformamide/ether).

b) A suspension of 860.1 mg of 4-(2-benzimidazolyl)-2-methoxy-6-nitrophenol in 10 ml of glacial acetic acid and 10 ml of 48 percent hydrobromic acid is heated to boiling under reflux for 72 hours. The mixture is then evaporated and the residue is treated four times with 50 ml of toluene each time, which is again distilled each time. There is obtained 5-(2-benzimidazolyl)-3-nitropyrocatechol of m.p. >300° (from acetone/water).

In an analogous manner:

c) From 4-(5,6-dichloro-2-benzimidazolyl)-2-methoxy-6-nitrophenol there is obtained 5-(5,6-dichloro-2-benzimidazolyl)-3-nitropyrocatechol of m.p. 282°-284° (from acetone/water).

EXAMPLE 30

A suspension of 29.0 g of 2-bromo-4'-hydroxy-3'-methoxy-5'-nitroacetophenone in 700 ml of dry methylene chloride is treated at −20° within 30 minutes with a solution of 125.3 g of boron tribromide in 300 ml of dry methylene chloride. After the addition the mixture is stirred at −20° for a further 1 hour and at room temperature for 16 hours, then evaporated, the residue is treated cautiously with water while cooling with ice and stirred at 50° for 30 minutes. After cooling the mixture is extracted with ether, the ethereal phase is washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone of m.p. 138°-140° (from methylene chloride).

EXAMPLE 31

a) A solution of 3.6 g of ethyl 3,4-dihydroxy-5-nitrophenylglyoxylate in 30 ml of acetic anhydride is heated at 110° for 30 minutes in the presence of a catalytic amount of conc. sulfuric acid, cooled to room temperature, the reaction mixture is poured into 150 ml of water and stirred for 60 minutes. The mixture is extracted with ether, washed with saturated sodium chloride solution, the combined organic extracts are dried sodium sulfate, filtered and evaporated. There is obtained ethyl 3,4-diacetoxy-5-nitrophenylglyoxylate of m.p. 87°-89° (from ether/petroleum ether).

In an analogous manner:

b) From 3-(3,4-dihydroxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one there is obtained 3-(3,4-diacetoxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one of m.p. 186°-188° (from methylene chloride/methanol).

c) from 3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone there is obtained 3-(3,4-diacetoxy-5-nitrophenyl)-2(1H)-quinoxalinone of m.p. 241°-243° (from methylene chloride/methanol),

d) from 3,4-dihydroxy-5-nitrobenzophenone there is obtained 3,4-diacetoxy-5-nitrobenzophenone of m.p. 141°-143° (from methylene chloride/ether),

e) from 2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone there is obtained 3,4-diacetoxy-2'-fluoro-5-nitrobenzophenone of m.p. 122°-124° (from ether) and

f) from 3,4-dihydroxy-5-nitrophenyl 4-pyridyl ketone there is obtained 3,4-diacetoxy-5-nitrophenyl 4-pyridyl ketone of m.p. 148°-150° (from methylene chloride/ether).

EXAMPLE 32

a) A solution of 2.0 g of 3,5-dinitropyrocatechol in 25 ml of propionic anhydride is heated at 110° for 18 hours in the presence of a catalytic amount of conc. sulfuric acid, the excess anhydride is distilled off at 70° in a high vacuum (1.33 Pa), the residue is dissolved in methylene chloride, washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 1,2-dipropionyloxy-3,5-dinitrobenzene of m.p. 74°-76° (from methylene chloride/petroleum ether).

In an analogous manner:

b) From 3-(3,4-dihydroxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one there is obtained 3-(3,4-dipropionyloxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one of m.p. 158°-160° (from methylene chloride),

c) from 6-chloro-3-(3,4-dihydroxy-5-nitrophenyl)-2H-1,4-benzoxazin-2-one there is obtained 5-(6-chloro-2-oxo-2H-1,4-benzoxazin-3-yl)-3-nitro-o-phenylene-dipropionate of m.p. 148°-150° 1 (from methylene chloride/ether),

d) from 3-(3,4-dihydroxy-5-nitrophenyl)-7-nitro-2H-1,4-benzoxazin-2-one there is obtained 3-nitro-5-(7-nitro-2-oxo-2H-1,4-benzoxazin-3-yl)-o-phenylene-dipropionate of m.p. 177°-179° (from methanol),

e) from 3-(3,4-dihydroxy-5-nitrophenyl)-2-oxo-2H-1,4-benzoxazine-6-carboxylic acid there is obtained 3-[3,4-benzoxazine-6-carboxylic acid there is obtained 3-[3,4-bis(propionyloxy)-5-nitrophenyl]-2-oxo-2H-1,4-benzoxazine-6-carboxylic acid of m.p. 192°-194° (from methylene chloride),

f) from 3-nitro-5-(2-quinoxalinyl)pyrocatechol there is obtained 3-nitro-5-(2-quinoxalinyl)-o-phenylenedipropionate of m.p. 152°-154° (from methylene chloride/ether,

g) from 5-(2-benzimidazolyl)-3-nitropyrocatechol there is obtained 5-(2-benzimidazolyl)-3-nitro-o-phenylenedipropionate of m.p. 179°-181° (from ether),

h) from 6,7-dichloro-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone there is obtained 5-(6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl)-3-nitro-o-phenylenedipropionate of m.p. 260°-262° (from methylene chloride),

i) from 5-bromo-2-(3,4-dihydroxy-5-nitrobenzoyl)-3-methylindole there is obtained 5-bromo-2-(3,4-dipropionyloxy-5nitrobenzoyl)-3-methylindole of m.p. 196°-198° (from ether) and

j) from 6-(3,4-dihydroxy-5-nitrophenyl)-3-mercapto-1,2,4-triazin-5(4H)-one there is obtained 3-nitro-5-(2,3,4,5-tetrahydro-5-oxo-3-thioxo-as-triazin-6-yl)-o-phenylenedipropionate of m.p. 237°-239° (from ether).

EXAMPLE 33

a) A solution of 1.09 g of ethyl 3,4-dihydroxy-5-nitrophenylglyoxylate in 6 ml of isobutyric anhydride is heated at 110° for 17 hours in the presence of a catalytic amount of conc. sulfuric acid. The reaction mixture is then treated ten times with 10 ml of toluene each time, whereby it is evaporated each time at 80° and 18.7 mbar. The oily residue is distilled in a bulb-tube at 175°-180° and 8.0 Pa. There is obtained ethyl 3,4-diisobutyryloxy-5-nitrophenylglyoxylate.

In an analogous manner:

b) From 3,5-dinitropyrocatechol there is obtained 1,2-diisobutyryloxy-3,5-dinitrobenzene of m.p. 78°-80° (from ether),

c) from 3-(3,4-dihydroxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one there is obtained 3-(3,4-diisobutyryl-oxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one of m.p. 142°-144° (from ether),

d) from 2-(3,4-dihydroxy-5-nitrophenyl)quinoxaline there is obtained 2-(3,4-diisobutyryloxy-5-nitrophenyl)-quinoxaline of m.p. 155°-157° (from ether),

e) from 1-methyl-3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone there is obtained 1-methyl-3-(3,4-diisobutyryloxy-5-nitrophenyl)-2(1H)-quinoxalinone of m.p. 138°-140° (from ether),

f) from 5-(imidazo[2,1-b]-1,3,4-thiadiazol-6-yl)-3-nitropyrocatechol there is obtained 5-(imidazo[2,1-b]-1,3,4-thiadiazol-6-yl)-3-nitro-o-phenylene diisobutyrate of m.p. 169°-171° (from methylene chloride),

g) from 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone there is obtained 5-(bromoacetyl)-3-nitro-o-phenylene diisobutyrate of m.p. 56°-58° (from methylene chloride/hexane),

h) from 5-(2-amino-4-thiazolyl)-3-nitropyrocatechol hydrobromide there is obtained 3-nitro-5-(2-isobutyramido-4-thiazolyl)-o-phenylene diisobutyrate of m.p. 157°-159° (from methylene chloride/ether),

i) from 5-(2-amino-6H-1,3,4-thiadiazin-5-yl)-3-nitropyrocatechol hydrobromide there is obtained 3-nitro-5-(2-isobutyramido-4-isobutyryl-1,3,4-thiadiazin-5-yl)-o-phenylene diisobutyrate of m.p. 177°-179° (from ether),

j) from 3-(3,4-dihydroxy-5-nitrophenyl)-6-propyl-2H-1,4-benzoxazin-2-one there is obtained 3-nitro-5-(2-oxo-6-propyl-2H-1,4-benzoxazin-3-yl)-o-phenylene diisobutyrate of m.p. 131°-133° (from methanol),

k) from 5-(imidazo[1,2-a]pyridin-3-yl)-3-nitropyrocatechol there is obtained 5-(imidazo[1,2-a]pyridin-3-yl)-3-nitro-o-phenylene diisobutyrate of m.p. 137°-139° (from ether),

l) from 5-(imidazo[2,1-b]benzothiazol-2-yl)-3-nitropyrocatechol there is obtained 5-(imidazo[2,1-b]benzothiazol-2-yl)-3-nitro-o-phenylene diisobutyrate of m.p. 197°-199° (from methylene chloride/ether and

m) from 3,4-dihydroxy-5-nitrophenyl 2-pyridyl ketone hydrobromide there is obtained 3-nitro-5-(2-pyridylcarbonyl)-o-phenylene diisobutyrate of m.p. 83°-85° (from ether/hexane).

EXAMPLE 34

a) A solution of 613.0 mg of ethyl 3,4-dihydroxy-5-nitrophenylglyoxylate in 4 ml of pivaloyl anhydride is heated to 100° for 17 hours in the presence of a catalytic amount of conc. sulfuric acid, the cooled solution is diluted with ether, washed with saturated sodium solution, dried over sodium sulfate, filtered and evaporated. The residue is treated ten times with 10 ml of toluene, whereby it is evaporated again each time. After bulb-tube distillation (air-bath) at 175°-180° and 4.0 Pa there is obtained ethyl 3,4-dipivaloxyloxy-5-nitrophenyl-glyoxylate.

In an analogous manner:

b) From 3-(3,4-dihydroxy-5-nitrophenyl)-6-methyl-2H-1,4-benzoxazin-2-one there is obtained 3-(3,4-dipivaloyloxy-5-nitrophenyl)-6-methyl-2H-benzoxazin-2-one of m.p. 180°-192° (from ether),

c) from 3,4-dihydroxy-5-nitrobenzophenone there is obtained 3,4-dipivaloyloxy-5-nitrobenzophenone of m.p. 101°-103° (from t-butyl methyl ether) and

d) from 2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone there is obtained 3,4-dipivaloyloxy-2'-fluorobenzophenone of m.p. 74°-76° (from low-boiling petroleum ether).

EXAMPLE 35

A solution of 1.7 g of 3-(3,4-dihydroxy-5-nitrophenyl)-2(1H)-quinoxalinone in 17 ml of octanoic anhydride is heated to 110° for 17 hours in the presence of a catalytic amount of conc. sulfuric acid, the excess anhydride is then distilled in a high vacuum, the residue is dissolved in methylene chloride, the organic solution is washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 5-(1,2-dihydro-3-oxo-3-quinoxalinyl)-3-nitro-o-phenylene diheptanoate of m.p. 186°-188° (from methylene chloride/ether).

EXAMPLE 36

a) 1.26 g of sodium acetate are added to a solution of 1.35 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone in 25 ml of alcohol and heated to boiling under reflux. After 6 hours, the reaction mixture is filtered from separated sodium bromide and evaporated. The residue is dissolved in ethyl acetate. The solution is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated at 50°. There is obtained (3,4-dihydroxy-5-nitrobenzoyl)methyl acetate of m.p. 166°-168° (from ethyl acetate/ether).

In an analogous manner:

b) from 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and sodium isobutyrate there is obtained (3,4-dihydroxy-5-nitrobenzoyl)methyl isobutyrate of m.p. 120°-122° (from ethyl acetate/ether) and

c) from 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and sodium 3,4-dihydroxy-5-nitrophenylglyoxylate there is obtained 3,4-dihydroxy-5-nitrophenacyl (3,4-dihydroxy-5-nitrobenzoyl)formate of m.p. 224°-226° (from methanol/ethyl acetate).

EXAMPLE 37

A suspension of 2.91 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 1.31 g of thionicotinamide in 50 ml of alcohol and heated to boiling under reflux for 2 hours. After cooling to room temperature the crystals are filtered under suction and recrystallized from N,N-dimethylformamide/alcohol. There is obtained 3-nitro-5-[2-(3-pyridyl)-4-thiazolyl]pyrocatechol of m.p. 279°-281°.

EXAMPLE 38

A solution of 552 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone and 2.7 g of 2-aminoacetophenone in 100 ml of dry N,N-dimethylformamide is stirred at 90° for 24 hours. The reaction mixture is evaporated, the residue is dissolved in ethyl acetate, washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 2-(3,4-dihydroxy-5-nitrobenzoyl)-3-methylindole of m.p. 212°-214° (from n-butanol).

EXAMPLE 39

A suspension of 7.32 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 4.06 g of 1-(3-pyridinyl)-2-thiourea in 100 ml of n-butanol and heated to boiling under reflux for 3 hours. After cooling to room temperature the crystals are filtered under suction and recrystallized from n-butanol. There is obtained 3-nitro-5-[2-(3-pyridylamino)-4-thiazolyl]pyrocatechol hydrobromide of m.p. >300°.

EXAMPLE 40

A suspension of 6.35 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 4.68 g of 1-(3-quinolinyl)-2-thiourea in 150 ml of n-butanol and heated to boiling under reflux for 3 hours. After cooling to room temperature the crystals are filtered under suction and recrystallized from n-butanol. There is obtained 3-nitro-5-[2-(3-quinolinylamino)-4-thiazolyl]pyrocatechol hydrobromide of m.p. >300°.

EXAMPLE 41

A suspension of 8.28 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 6.37 g of rac-1-(2-exo-bornyl)-2-thiourea in 100 ml of n-butanol and heated to boiling under reflux for 3 hours. After cooling to room temperature the crystals are filtered under suction and recrystallized from n-butanol. There is obtained rac-3-nitro-5-[2-(2-exo-bornylamino)-4-thiazolyl]-pyrocatechol hydrobromide of m.p. 262°-264°.

EXAMPLE 42

0.875 ml of pyrrolidine in 35 ml of tetrahydrofuran is treated at 5° with 0.605 ml of acetic acid and subsequently with 1.73 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.87 g of 6-oxo-4'-(trifluoromethyl)-heptananilide and stirred at 23° under argon for 56 hours. The residue obtained after evaporating the reaction mixture is partitioned between ethyl acetate and 1N sodium hydroxide solution. The combined sodium hydroxide extracts are made acid with conc. hydrochloric acid, extracted with ethyl acetate, the combined ethyl acetate extracts are washed with saturated sodium chloride solution, dried over sodium sulfate, evaporated and the residue is chromatographed on 120 g of silica gel with methylene chloride/methanol (91:9). After recrystallization from ethyl acetate/petroleum ether there is obtained (E)-8-(3,4-dihydroxy-5-nitrophenyl)-6-oxo-4'-(trifluoromethyl)-7-octenanilide of m.p. 194°-197°.

EXAMPLE 43

a) 26.0 g of 2-chloro-3-hydroxy-p-anisaldehyde are dissolved in 400 ml of acetic anhydride and 5 ml of pyridine. The solution is stirred at 80° for 8 hours, subsequently evaporated, the residue is partitioned between ice-water and methylene chloride, the organic phase is dried over sodium sulfate, evaporated and the residue is recrystallized from methylene chloride/petroleum ether. There is obtained 2-chloro-3-formyl-6-methoxyphenyl acetate of m.p. 48°-50°.

b) 38 g of 2-chloro-3-formyl-6-methoxyphenyl acetate are introduced portionwise at −5° to −10° within 15 minutes into 150 ml of 98 percent nitric acid. After stirring at −5° for 30 minutes the reaction mixture is poured into 1.5 l of ice-water and extracted three times with 500 ml of methylene chloride. The combined organic phases are washed with ice-water, dried over sodium sulfate and evaporated. The residue is crystallized from ether. There is obtained 2-chloro-3-formyl-6-methoxy-5-nitrophenyl acetate of m.p. 84°-85°.

c) 35.8 g of 2-chloro-3-formyl-6-methoxy-5-nitrophenyl acetate are dissolved in 300 ml of methanol. After adding 145 ml of 1N sodium hydroxide solution the mixture is stirred at 23° for 1 hour. After evaporation of the methanol, the residue is diluted with ice-water, made acid with 2N hydrochloric acid and extracted twice with 400 ml of ethyl acetate each time. The organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue is recrystallized from methylene chloride/petroleum ether. There is obtained 2-chloro-3-hydroxy-5-nitro-p-anisaldehyde of m.p. 130°.

d) 1.3 g of 2-chloro-3-hydroxy-5-nitro-p-anisaldehyde are dissolved in 80 ml of methylene chloride, treated with 0.82 ml of boron tribromide, stirred at 23° for 18 hours, the reaction mixture is treated with 5 ml of methanol while cooling with ice, evaporated, the residue is dried in a high vacuum, digested in water, filtered and recrystallized from acetonitrile. There is obtained 2-chloro-3,4-dihydroxy-5-nitrobenzaldehyde of m.p. 193°-195°.

EXAMPLE 44

a) A mixture of 30 g of 2-chloro-3-hydroxy-p-anisaldehyde and 230 ml of ethanol is stirred at 70° for 4 hours in the presence of 12.3 g of hydroxylamine hydrochloride, the reaction mixture is subsequently evaporated, the residue is dried in a high vacuum and recrystallized from methanol/water. There is obtained 2-chloro-3-hydroxy-p-anisaldehyde oxime of m.p. 174°-176°.

b) 21 g of 2-chloro-3-hydroxy-p-anisaldehyde oxime are heated under reflux for 20 hours together with 400 ml of acetic anhydride. Thereupon, the reaction mixture is evaporated, the residue is treated with 300 ml of ice-water, stirred for 1 hour, decanted, the thus-cooled residue is partitioned between methylene chloride and water, the organic phase is dried over sodium sulfate, evaporated, the residue is dried in a high vacuum, chromatographed on 200 g of silica gel with methylene chloride and recrystallized from methylene chloride/-petroleum ether. There is obtained 2-chloro-3-cyano-6-methoxyphenyl acetate of m.p. 97°-99°.

c) In analogy to Examples 43b and 43c, from 2-chloro-3-cyano-6-methoxyphenyl acetate there is obtained 2-chloro-3-hydroxy-5-nitro-p-anisonitrile of m.p. 157°-159° (methylene chloride/hexane).

d) In analogy to Example 43d, from 2-chloro-3-hydroxy-5-nitro-p-anisonitrile there is obtained 2-chloro-3,4-dihydroxy-5-nitro-benzonitrile of m.p. 180° (acetonitrile).

EXAMPLE 45

a) 5.5 g of α-chloro-2-fluoro-3,4-dimethoxytoluene and 4.05 g of potassium acetate are stirred at 80° for 25 hours in 50 ml of dimethylformamide. The reaction mixture is subsequently poured into 150 ml of ice-water and extracted with ether. The ether phases are washed with sodium chloride solution, dried over sodium sulfate and evaporated, 2-fluoro-3,4-dimethoxybenzyl acetate is obtained as an oil.

b) 5.4 g of 2-fluoro-3,4-dimethoxybenzyl acetate are heated to 80° for 1.5 hours together with 50 ml of methanol and 50 ml of 1N sodium hydroxide solution. After evaporation of the methanol the residue is extracted with methylene chloride. The combined extracts are washed with water, dried over sodium sulfate and evaporated. The residue is chromatographed on 80 g of silica gel with methylene chloride/methanol (95:5). 2-fluoro-3,4-dimethoxybenzyl alcohol is obtained as an oil.

c) 3.0 g of 2-fluoro-3,4-dimethoxybenzyl alcohol and 5.0 g of manganese dioxide are heated under reflux for 1 hour together with 50 ml of benzene. The insoluble constituents are subsequently filtered while washing with methylene chloride. The filtrate is evaporated and the residue is recrystallized from methylene chloride/-hexane. There is obtained 2-fluoro-3,4-dimethoxybenzaldehyde of m.p. 52°-54°.

d) 4.4 g of 2-fluoro-3,4-dimethoxybenzaldehyde and 1.83 g of hydroxylamine hydrochloride are heated under reflux for 5 hours together with 30 ml of ethanol. The reaction mixture is subsequently evaporated and the residue, dried in a high vacuum at 23°, is introduced into 40 ml of phosphorus oxychloride. After stirring at 23° for 2.5 hours the reaction mixture is evaporated, the residue is treated with ice-water, the precipitate which thereby forms is filtered off, washed with water, taken up in methylene chloride, the methylene chloride solution is dried over sodium sulfate and evaporated. By recrystallization of the residue from methylene chloride/hexane there is obtained 2-fluoro-3,4-dimethoxybenzonitrile of m.p. 64°-65°.

e) 2.0 g of 2-fluoro-3,4-dimethoxybenzonitrile are dissolved in 60 ml of methylene chloride, treated with 1.1 ml of boron tribromide, stirred at 23° for 1 hour, subsequently treated with an additional 1.0 ml of boron tribromide and stirred at 23° for an additional 80 minutes. Thereupon, the reaction mixture is poured into 100 ml of ice-cold saturated sodium hydrogen carbonate solution, whereupon the mixture is extracted twice with 300 ml of ether, the combined ether phases are washed twice with sodium chloride solution, dried over sodium sulfate, evaporated and the residue is chromatographed on 50 g of silica gel with methylene chloride and methylene chloride/methanol (97:3). There is obtained 2-fluoro-3-hydroxy-p-anisonitrile of m.p. 198°-200°.

f) 0.9 g of 2-fluoro-3-hydroxy-p-anisonitrile are dissolved in 10 ml of acetic anhydride and 0.5 ml of pyridine, whereupon the mixture is stirred at 120° for 2 hours. The reaction mixture is subsequently evaporated and the residue is partitioned between ice-water and methylene chloride. The organic phase is dried over sodium sulfate and evaporated, and the residue is recyrstallized from methylene chloride/hexane. There is obtained 3-cyano-2-fluoro-6-methoxyphenyl acetate of m.p. 90°-91°.

g) 0.8 g of 3-cyano-2-fluoro-6-methoxyphenyl acetate are introduce din three portions at −15° into 5 ml of 96 percent nitric acid, whereupon the mixture is stirred at −10° for 1 hour. Thereupon, the reaction mixture is poured on to 50 g of ice. The mixture is extracted twice with 70 ml of ethyl acetate each time. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The thus-obtained residue is dissolved in 50 ml of 1N sodium carbonate solution and 50 ml of methanol, whereupon the solution is stirred at 23° for 1 hour and the methanol is distilled off. The residal aqueous phase is adjusted to pH 2 at 0° with conc. hydrochloric acid and extracted twice with 100 ml of ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated, and the residue is chromatographed on 45 g of silica gel with methylene chloride/methanol (97:3). After recrystallization from ether/hexane there is obtained 2-fluoro-3-hydroxy-5-nitro-p-anisonitrile of m.p. 112°-113°.

h) 550 mg of 2-fluoro-3-hydroxy-5-nitro-p-anisonitrile are dissolved in 30 ml of methylene chloride, whereupon the solution is treated with 0.44 ml of boron tribromide. After stirring at 23° for 6 hours an additional 0.1 ml of boron tribromide are added thereto, whereupon the mixture is stirred at 23° for an additional 1.5 hours. Thereupon, 3 ml of ethanol are added thereto at −15°. The reaction mixture is evaporated and the residue is dried in a high vacuum at 23°. By recrystallization from ether/hexane there is obtained 2-fluoro-3,4-dihydroxy-5-nitrobenzonitrile of m.p. 154°.

EXAMPLE 46

a) 9.5 g of 3,4-dimethoxy-5-nitrobenzoic acid are suspended in 95 ml of thionyl chloride. The suspension is stirred at 80° for 1 hour. By two-fold evaporation with the addition of absolute toluene there are obtained 10 g of 3,4-dimethoxy-5-nitrobenzoyl chloride which is dissolved in 100 ml of tetrahydrofuran. This solution is added dropwise to 300 ml of 28 percent aqueous ammo-

nia. The mixture is subsequently stirred at 40° for 2 hours and cooled to 5°. The crystalline precipitate is filtered off. There is obtained 3,4-dimethoxy-5-nitrobenzamide of m.p. 182°–185°.

b) 2.46 g of chlorine are introduced while cooling with ice into a mixture of 8.0 g of sodium hydroxide, 50 ml of water and 30 g of ice. Thereupon, 6.5 g of 3,4-dimethoxy-5-nitrobenzamide suspended in 5 ml of tetrahydrofuran are slowly added thereto. The reaction mixture is heated to 70° within 30 minutes, stirred at 70° for 1 hour, cooled to 5° and the separated crystals are filtered off. There is obtained 3,4-dimethoxy-5-nitroaniline of m.p. 129°–131°. By extraction of the filtrate with ethyl acetate, drying the extract over sodium sulfate, concentration and crystallization of the residue with the addition of ether there can be obtained an additional portion of 3,4-dimethoxy-5-nitroaniline.

c) 10 g of finely powdered 3,4-dimethoxy-5-nitroaniline are suspended in 15 ml of 12N hydrochloric acid and 40 ml of water, whereupon the suspension is stirring at 30° for 1 hour. Thereupon, 3.8 g of sodium nitrite dissolved in 20 ml of water are added dropwise thereto at −5° within 15 minutes. The solution is stirred at −5° for 30 minutes and the cold diazonium salt solution is added dropwise within 45 minutes to 100 ml of pyridine of 40°. The mixture is subsequently stirred at 70° for 1 hour. The reaction mixture is evaporated and the residue is taken up in 300 ml of ethyl acetate. It is extracted three times with 200 ml of 2N hydrochloric acid each time. The acidic-aqueous phase is adjusted to pH 9 with conc. ammonia and extracted with methylene chloride. The combined methylene chloride extracts are dried over sodium sulfate and evaporated, and the residue is chromatographed on 250 g of silica gel with ethyl acetate. After crystallization from methylene chloride/hexane there is obtained 2-(3,4-dimethoxy-5-nitrophenyl)-pyridine of m.p. 89°–90°.

d) 1.5 g of 2-(3,4-dimethoxy-5-nitrophenyl)pyridine are dissolved in 30 ml of 48 percent aqueous hydrobromic acid. The reaction mixture is stirred at 100° for 16 hours and at 23° for 18 hours. The precipitate which thereby forms is filtered and recrystallized from methanol/ether. There is obtained 3-nitro-5-(2-pyridyl)-pyrocatechol hydrobromide of m.p. 230°–240°.

EXAMPLE 47

a) 2.76 ml of 2-bromopyridine dissolved in 30 ml of absolute tetrahydrofuran are treated −60° within 30 minutes with 19.2 ml of 1.6M n-butyl lithium solution (in hexane), whereupon the mixture is stirred at −60° for 30 minutes. 6.0 g of 3,4-dimethoxy-5-nitrobenzaldehyde dissolved in 50 ml of tetrahydrofuran are then added dropwise thereto at −40° within 30 minutes. The reaction mixture is warmed to 0° within 2 hours, poured into ice-water and extracted with ethyl acetate. The combined extracts are dried over sodium sulfate and evaporated, and the residue is chromatographed on 200 g of silica gel with ethyl acetate. There is obtained α-(3,4-dimethoxy-5-nitrophenyl)-2-pyridinemethanol as a brown oil.

b) 7 g of manganese dioxide and added portionwise to 4.0 g of α-(3,4-dimethoxy-5-nitrophenyl)-2-pyridinemethanol dissolved in 100 ml of acetone while constantly heating under reflux over a period of 2.5 hours. Thereupon, the mixture is heated under reflux for an additional 2 hours. The manganese salts are subsequently filtered and the residue obtained after evaporation is recrystallized from ether/hexane. There is obtained 3,4-dimethoxy-5-nitrophenyl 2-pyridyl ketone of m.p. 113°.

c) 1.5 g of 3,4-dimethoxy-5-nitrophenyl-2-pyridyl ketone dissolved in 30 ml of 48 percent hydrobromic acid are stirred at 100° for 18 hours. Thereupon, the reaction mixture is evaporated and the residue is recrystallized from acetonitrile/methanol. There is obtained 3,4-dihydroxy-5-nitrophenyl 2-pyridyl ketone hydrobromide of m.p. 213°.

EXAMPLE 48

a) 11.3 g of tin dichloride dihydrate are added to 2.25 g of 3',4'-dimethoxy-5'-nitroacetophenone dissolved in 50 ml of ethanol, whereupon the mixture is stirred at 74° for 30 minutes. Thereupon, the reaction mixture is poured on to 100 g of ice, neutralized with about 300 ml of saturated sodium hydrogen carbonate solution and treated with 150 ml of methylene chloride. The mixture is filtered and the methylene chloride phase is separated. This is dried over sodium sulfate and evaporated, and the residue is recrystallized from ether/petroleum ether. There is obtained 5'-amino-3',4'-dimethoxyacetophenone of m.p. 63°–65°.

b) A solution of 5.2 g of sodium nitrile in 20 ml of water is added dropwise at 0° within 20 minutes to 14.0 g of 5'-amino-3',4'-dimethoxyacetophenone dissolved in 155 ml of 1N hydrochloric acid. After stirring at −2° for 30 minutes the cold diazonium salt solution is added dropwise within 30 minutes at 5°–10° to a solution of 8.7 g of copper(I) cyanide and 5.45 g of potassium cyanide in 60 ml of water. After completion of the addition 200 ml of methylene chloride are added, and the reaction mixture is stirred at 23° for 3 hours and then filtered. The organic phase is separated, washed with water, dried over sodium sulfate and evaporated. The residue is recrystallized from methylene chloride/petroleum ether. There is obtained 5'-cyano-3',4'-dimethoxyacetophenone of m.p. 125°–126°.

c) 3.75 g of aluminum powder and 28.5 g of iodine are heated under reflux for 2 hours in 160 ml of absolute benzene. 3.0 g of 5'-cyano-3',4'-dimethoxyacetophenone and 0.5 g of tetra-n-butylannomium iodide are then added at 20°, whereupon the mixture is heated under reflux for 1 hour. Thereupon, the mixture is treated at 20° with 50 g of ice and filtered. The residue is washed with ethyl acetate. The phases are separated and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with 20 percent sodium thiosulfate solution, dried over sodium sulfate and evaporated. The thus-obtained residue is dissolved in 20 ml of acetic anhydride and 0.5 ml of pyridine and stirred at 120° for 6 hours. The mixture is subsequently evaporated and the residue is partitioned between methylene chloride and ice-water. The methylene chloride phase is dried over sodium sulfate and evaporated, and the residue is chromatographed on 100 g of silica gel with methylene chloride. After recrystallization from ether there is obtained 5'-cyano-3',4'-diacetoxyacetophenone of m.p. 76°–79°.

EXAMPLE 49

0.33 g of 5'-cyano-3',4'-diacetoxyacetophenone dissolved in 3.3 ml of methanol is treated with 2.7 ml of 1.0N sodium hydroxide solution and the reaction mixture is stirred at 23° for 45 minutes. The mixture is subsequently acidified with 2N hydrochloric acid, diluted with 5 ml of saturated sodium chloride solution and extracted twice with 30 ml of ethyl acetate each time

The combined ethyl acetate phases are dried over sodium sulfate and evaporated. The residue is recrystallized from toluene/acetonitrile. There is obtained 5'-cyano-3',4'-dihydroxyacetophenone as brownish crystals which decompose which decompose above 215°.

EXAMPLE 50

a) 3.48 g of phenyltrimethylammonium bromide dibromide dissolved in 30 ml of tetrahydrofuran are added dropwise at room temperature within 45 minutes to 1.9 g of 5'-cyano-3',4'-dimethoxyacetophenone dissolved in 30 ml of tetrahydrofuran, whereupon the mixture is stirred for 30 minutes. Thereupon, the reaction mixture is poured into 120 ml of ice-water and extracted three times with 70 ml of methylene chloride. The combined methylene chloride phases are washed with 2N sulfuric acid, dried over sodium sulfate and evaporated. The residue is chromatographed on 20 g of silica gel with methylene chloride. After recrystallization from methylene chloride/hexane there is obtained 5-(bromoacetyl)-2,3-dimethoxybenzonitrile of m.p. 138°-141°.

b) 1.45 g of 5-(bromoacetyl)-2,3-diethoxybenzonitrile and 1.12 g of selenium dioxide are stirred at 120° for 18 hours in 10 ml of n-hexanol. After cooling to room temperature the mixture is diluted with 20 ml of methylene chloride and filtered. The filtrate is washed with water, dried over sodium sulfate and evaporated. The residue is chromatographed on 70 g of silica gel with hexane/ether (2:1). there is obtained hexyl (3-cyano-4,5-dimethoxyphenyl)glyoxylate as an oil.

c) 4.8 ml of boron tribromide dissolved in 20 ml of methylene chloride are added dropwise while cooling with ice within 20 minutes to 4.0 g of hexyl (3-cyano-4,5-dimethoxyphenyl)glyoxylate dissolved in 100 ml of methylene chloride and the reaction mixture is stirred at room temperature for 18 hours. 40 ml of methanol are subsequently added dropwise thereto at −60°, the mixture is stirred at room temperature for 1 hour and evaporated. The residue is taken up in methanol. It is heated under reflux for 10 minutes, evaporated to dryness and dried in a high vacuum. The thus-obtained crude product is recrystallized from acetonitrile. There is obtained methyl (3-cyano-4,5-dihydroxyphenyl)glyoxylate of m.p. 252°.

EXAMPLE 51

1.075 g of methyl (3-cyano-4,5-dihydroxyphenyl)-glyoxylate and 0.60 g of 2-amino-p-cresol are stirred at 120° for 70 minutes in 2 ml of dimethylformamide. The mixture is subsequently cooled to room temperature and diluted with 15 ml of water. The precipitate is filtered and dried in a water-jet vacuum at 80° for 6 hours. After recrystallization from acetonitrile there is obtained 2,3-dihydroxy-5-(6-methyl-2-oxo-2H-1,4-benzoxazin-3-yl)benzonitrile of m.p. 278°-280°.

EXAMPLE 52

a) A solution of 2.5 g of 3,4-dimethoxy-5-nitrobenzoyl chloride in 10 ml of absolute tetrahydrofuran is treated with 1.1 ml of ethyl isocyanoacetate and subsequently with a solution of 3.0 ml of triethylamine in 10 ml of tetrahydrofuran and stirred at room temperature for 48 hours. After distillation of the solvent, the residue is extracted with ethyl acetate/water. The crude product obtained after evaporation is chromatographed on a 20-fold amount of silica gel with ethyl acetate. After recrystallization from ethyl acetate/hexane there is obtained ethyl 5-(3,4-dimethoxy-5-nitrophenyl)-4-oxazolecarboxylate in the form of yellow crystals of m.p. 109°-110°.

b) 1.0 g of ethyl 5-(3,4-dimethoxy-5-nitrophenyl)-4-oxazolecarboxylate is treated with 10 ml of constant-boiling hydrobromic acid and stirred at 140° for 2 hours. After distillation of the excess hydrobromic acid, the yellow residue is recrystallized from ethanol/acetone. There is obtained 2-amino-3',4'-dihydroxy-5'-nitroacetophenone hydrobromide in the form of yellow crystals of m.p. >250° (dec.).

EXAMPLE 53

a) 10 g of ethyl (3,4-dimethoxy-5-nitrobenzoyl)acetate are suspended in 100 ml of ethanol, treated with 1.7 g of methylhydrazine and heated under reflux for 16 hours. After distillation of about 50 ml of ethanol, the mixture is cooled to 0° and the separated precipitate is filtered under suction. After recrystallization from ethanol there is obtained 3-(3,4-dimethoxy-5-nitrophenyl)-1-methylpyrazol-5-ol in the form of yellow crystals of m.p. 200°-202°.

b) 2.0 g of 3-(3,4-dimethoxy-5-nitrophenyl)-1-methylpyrazol-5-ol are suspended in 100 ml of methylene chloride. After cooling to −40° a solution of 4.9 ml of boron tribromide in 60 ml of methylene chloride is added dropwise thereto within 1 hour. The mixture is subsequently stirred at room temperature for 16 hours, cooled to −20° and treated within 30 minutes with 100 ml of ethanol. After stirring at room temperature for 1 hour, the solvent is removed by distillation in a water-jet vacuum at 40°. The residue is treated three times with a mixture of 100 ml of ethanol/toluene each time, with the solvent being distilled each time. The residue is recrystallized from ethanol. There is obtained 5-(5-hydroxy-1-methylpyrazol-3-yl)-3-nitropyrocatechol hydrobromide int he form of yellow crystals of m.p. >250°.

EXAMPLE 54

a) 16.8 g (0.7 g-atom) of magnesium are treated with 15 ml of ethanol and, after adding 2 ml of carbon tetrachloride, the reaction is initiated by heating. A solution of 130.3 g of tert.butyl ethyl malonate in 70 ml of ethanol and 600 ml of absolute ether is added dropwise thereto while stirring within about 30 minutes so that the reaction proceeds at the reflux temperature. The mixture is subsequently stirred at 50° for an additional 3 hours and the solvent is distilled at 40° in a water-jet vacuum. The residue is dissolved in 900 ml of tetrahydrofuran. To this solution is added dropwise while stirring at 50° a solution of 170 g of 3,4-dimethoxy-5-nitrobenzoyl chloride in 700 ml of absolute tetrahydrofuran and the mixture is stirred at the reflux temperature for 1 hour. The solvent is distilled at 40° in a water-jet vacuum. The residue is treated with 1 l of ether. 260 ml of 3N sulfuric acid are added thereto while cooling and stirring and the mixture is stirred for 30 minutes. The aqueous phase is extracted twice with 600 ml of ether each time. The organic phase is washed neutral with water, dried over sodium sulfate and evaporated. The brown oil obtained is filtered over 1 kg of silica gel with toluene. The resulting mixture, consisting of ethyl tert.-butyl (3,4-dimethoxy-5-nitrobenzoyl)malonate and ethyl (3,4-dimethoxy-5-nitrobenzoyl)acetate, is dissolved in 600 ml of methylene chloride and treated while stirring within about 30 minutes with 193 ml of trifluoracetic acid. The mixture is subsequently stirred

at 40° for 2 hours and then evaporated at 40° in a water-jet vacuum. The oil obtained is extracted with ether/-water. The organic phase is dried over sodium sulfate and evaporated. After dissolution in diisopropyl ether/-hexane and cooling the separated crystals are filtered under suction and recrystallized from diisopropyl ether. There is obtained ethyl (3,4-dimethoxy-5-nitrobenzoyl-)acetate in the form of slightly yellowish crystals of m.p. 67°-68°.

b) 10.0 g of ethyl (3,4-dimethoxy-5-nitrobenzoyl)acetate are reacted with 4.0 g of phenylhydrazine in analogy to Example 53a. After recrystallization from methylene chloride/ethanol, there is obtained 3-(3,4-dimethoxy-5-nitrophenyl)-1-phenyl-2-pyrazolin-5-one in the form of yellow crystals of m.p. 190°-192°.

c) In analogy to Example 53b, with boron tribromide there is obtained therefrom 5-(5-hydroxy-1-phenyl-pyrazol-3-yl)-3-nitropyrocatechol hydrobromide in the form of yellow crystals of m.p. >220° (dec.).

EXAMPLE 55

20.1 g of diethyl (3,4-dimethoxy-5-nitrobenzoyl)malonate are dissolved in 200 ml of methylene chloride, whereupon the solution is cooled to −20° and at this temperature there is added dropwise while stirring within 15 minutes a solution of 68.1 g of boron tribromide in 120 ml of methylene chloride. The mixture is subsequently stirred at room temperature overnight. After cooling to −20°, the mixture is treated with 300 ml of ethanol and stirred at room temperature for 30 minutes. The solvent is distilled in a water-jet vacuum at 40°. The residue is treated with 300 ml of ice-water and methylene chloride. The organic phase is washed with water, dried over sodium sulfate and evaporated. The crude product obtained is chromatographed on a 10-fold amount of silica gel with toluene. After crystallization from methylene chloride/hexane there is obtained ethyl (3,4-dihydroxy-5-nitrobenzoyl)acetate in the form of yellow crystals of m.p. 136°-137°.

EXAMPLE 56

2.0 g of ethyl (3,4-dihydroxy-5-nitrobenzoyl)acetate are suspended in 50 ml of ethanol. After treatment with 0.4 g of hydrazine hydrate the mixture is held at the reflux temperature for 16 hours. After distillation of the solvent, the residue is held at the boiling temperature for 5 minutes with 50 ml of ethyl acetate. The separated precipitate is filtered under suction and the filtrate is concentrated to 10 ml. The crystals, which separate in the cold, are filtered under suction. There is obtained 5-(5-hydroxypyrazol-3-yl)-3-nitropyrocatechol in form of orange crystals of m.p. 228° (dec.).

EXAMPLE 57

7.3 g of 3,4-dihydroxy-5-nitrobenzoic acid are treated with 30 ml of acetic anhydride, whereupon the mixture is held at the reflux temperature for 8 hours. The reaction mixture is poured on to ice. The separated precipitate is filtered under suction, washed with water and taken up in methylene chloride. The organic phase is dried over sodium sulfate and evaporated. The residue obtained is recrystallized from methylene chloride/n-hexane in the cold. There is obtained 3,4-diacetoxy-5-nitrobenzoic acid in the form of colorless crystals of m.p. 126°-127°.

EXAMPLE 58

a) 9.7 g of 3,4-diacetoxy-5-nitrobenzoic acid are treated with 12.5 ml of thionyl chloride, whereupon the mixture is stirred at 100° for 1.5 hours. After distillation of the excess thionyl chloride, the 5-(chloro-carbonyl)-2-nitro-o-phenylene diacetate is distilled, b.p. 160° (26.7 Pa).

b) 3.2 g of 5-(chlorocarbonyl)-2-nitro-o-phenylene diacetate are dissolved in 50 ml of dimethylformamide. The ice-cold solution is treated while stirring with a solution of 2.2 ml of diethylamine in 20 ml of dimethylformamide. The mixture is subsequently stirred at room temperature for 1 hour, whereupon the solvent is distilled in a water-jet vacuum at 50°. The residue obtained is treated with water and methylene chloride. The organic phase is dried over sodium sulfate and evaporated. The yellow resin obtained is crystallized from methylene chloride/ether. There is obtained N,N-diethyl-3,4-dihydroxy-5-nitrobenzamide in the form of yellow crystals of m.p. 145°-146°.

EXAMPLE 59

3.2 g of 5-(chlorocarbonyl)-2-nitro-o-phenylenediacetate are dissolved in 50 ml of dimethylformamide, whereupon the solution is treated at 0°-5° while stirring and within 40 minutes with a solution of 3.02 ml of 2,2-diethylaminoethylamine in 20 ml dimethylformamide. The mixture is subsequently stirred at room temperature for 30 minutes. The solvent is distilled in a water-jet vacuum at 60°. The residue is extracted twice with 20 ml of ethanol each time, dissolved in hot ethanol and treated with an excess of ethanolic hydrochloric acid, whereupon the mixture is evaporated. After recrystallization from ethanol/ethyl acetate there is obtained N-[2-(diethylamino)ethyl]-3,4-dihydroxy-5-nitrobenzamide hydrochloride in the form of yellow crystals of m.p. 139° (dec.).

EXAMPLE 60

a) 10.0 g of 2,3-dimethoxy-5-nitrobenzaldehyde are treated with 50 ml of glacial acetic acid and 50 ml of constant-boiling hydrobromic acid and held at the reflux temperature for 7 hours. After treatment with ice the separated precipitate is filtered under suction, washed with water and taken up in ethyl acetate. The organic phase is dried over sodium sulfate and evaporated. The crude product obtained is filtered over silica gel with ethyl acetate. After crystallization from ethyl acetate/hexane there is obtained 2,3-dihydroxy-5-nitrobenzaldehyde in the form of brownish crystals of m.p. 226°-228°.

b) 4.5 g of 2,3-dihydroxy-5-nitrobenzaldehyde are suspended in 75 ml of water. After treatment with 4.2 g of hydroxylamine o-sulphonic acid, the mixture is stirred at 65° for 16 hours. After cooling the separated crystals are filtered under suction and washed with water. The filtrate is extracted with ethyl acetate. The crystals and the dried organic phase are combined, whereupon the mixture is evaporated and the residue is recrystallized from diisopropyl ether. There is obtained 2,3-dihydroxy-5-nitrobenzonitrile in the form of yellow crystals of m.p. 186°-188°.

EXAMPLE 61

a) 4.0 g of 3,4-dimethyoxy-5-nitro-benzonitrile are dissolved in 50 ml of dimethylformamide, whereupon the solution is treated with 1.66 g of ammonium chlo-

ride and 2.02 g of sodium azide and stirred at 125° for 31 hours. After in each case 8 and 15 hours the same amounts of ammonium chloride and sodium azide are added thereto. After cooling the mixture is poured on to ice. The separated precipitate is filtered under suction, washed with water and dried. There is obtained 2-methoxy-6-nitro-4-(1H-tetrazol-5-yl)phenol in the form of orange crystals of m.p. >240° (dec.).

b) 4.0 g of 2-methoxy-6-nitro-4-(1H-tetrazol-5-yl)phenol are treated with 40 ml of constant-boiling hydrobromic acid, whereupon the mixture is stirred at 140° for 8 hours under a nitrogen atmostphere. After cooling, the mixture is poured on to ice. The separated precipitate is filtered under suction and recrystallized from ether. There is obtained 3-nitro-5-(1H-tetrazol-5-yl)-pyrocatechol in the form of orange crystals of m.p. >240° (dec.).

EXAMPLE 62

A total of 7.2 g of 3,4-dihydroxy-5-nitro-benzonitrile are introduced portionwise into 130 ml of conc. sulfuric acid while stirring within 10 minutes, whereupon the mixture is stirred at 50° for 4 hours. The reaction mixture is poured into 800 ml of ice-water. The separated precipitate is filtered under suction, washed with water and taken up in ethyl acetate. The organic phase is dried over sodium sulfate and evaporated. After recrystallization from acetone/ethyl acetate there is obtained 3,4-dihydroxy-5-nitrobenzamide in the form of orange crystals of m.p. 235°-236°.

EXAMPLE 63

a) A solution of 11.25 g of 2-hydroxyacetophenone in 100 ml of absolute dimethylformamide is added dropwise under an argon atmosphere within 15 minutes to a suspension of 3.6 g of a 55 percent sodium hydride dispersion in 50 ml of absolute dimethyformamide and the mixture is stirred at room temperature for 1 hour. After cooling to 0°, a solution of 20.3 g of 3,4-dimethoxy-5-nitrobenzoyl chloride in 100 ml of absolute dimethylformamide is added dropwise thereto within 20 minutes and the mixture is stirred at room temperature overnight. The reaction mixture is poured into ice-water, whereupon the mixture is extracted twice with 250 ml of ethyl acetate each time. The organic phase is extracted twice with 100 ml of sodium chloride solution each time, dried over sodium sulfate and evaporated. The brown oil obtained is heated in 100 ml of toluene. The separated precipitate is filtered under suction and the filtrate is chromatographed on a 30-fold amount of silica gel with toluene/ethyl acetate (4:1). After recrystallization from ethyl acetate/hexane there is obtained o-acetylphenyl 3,4-dimethoxy-5-nitrobenzoate in the form of yellowish crystals of m.p. 108°-109°.

b) 10.0 g of o-acetylphenyl 3,4-dimethoxy-5-nitrobenzoate are dissolved in 50 ml of pyridine. After treatment with 8.12 g of powdered and dried potassium hydroxide, the mixture is stirred at 80° for 5 minutes. After cooling the mixture is poured on to ice. The aqueous solution is made acid by treatment with 3N hydrochloric acid. The separated precipitate is removed by filtration under suction. After recrystallization from ethyl acetate/hexane, there is obtained 1-(o-hydroxyphenyl)-3-(3,4-dimethoxy-5-nitrophenyl)-1,3-propanedione in the form of yellowish crystals of m.p. 188°-189°.

c) A solution of 1.82 g of boron tribromide in 20 ml of methylene chloride is added dropwise within about 20 minutes to a solution of 500 mg of 1-(o-hydroxyphenyl)-3-(3,4-dimethoxy-5-nitrophenyl)-1,3-propanedione in 50 ml of methylene chloride while stirring and under an argon atmosphere at −20°, whereupon the mixture is stirred at room temperature overnight. After cooling to −20° the mixture is treated dropwise with 25 ml of ethanol and evaporated at 40° in a water-jet vacuum. After recrystallization from ethanol, there is obtained 1-(3,4-dihydroxy-5-nitrophenyl)-3-(o-hydroxyphenyl)-1,3-propanedione in the form of yellow crystals of m.p. 251°-252°.

EXAMPLE 64

a) A solution of 2.0 g of o-acetylphenyl 3,4-dimethoxy-5-nitrobenzoate in 12.5 ml of glacial acetic acid is treated with 0.94 g of sodium acetate and held at the reflux temperature for 4 hours. After cooling the mixture is poured into ice-water. The separated crystals are filtered under suction. After recrystallization from ethyl acetate/hexane there is obtained 2-(3,4-dimethoxy-5-nitrophenyl)-4H-1-benzopyran-4-one in the form of colorless crystals of m.p. 216°-217°.

b) A solution of 10 ml of boron tribromide in 50 ml of methylene chloride are added dropwise within 30 minutes at −10° to a solution of 1.0 g of 2-(3,4-dimethoxy-5-nitrophenyl)-4H-1-benzopyran-4-one in 100 ml of methylene chloride under an argon atmosphere, whereupon the mixture is stirred at room temperature overnight. After cooling to −20°, 20 ml of ethanol are added dropwise thereto. The mixture is then evaporated in a water-jet vacuum. The yellow residue obtained is extracted with water/ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and evaporated. After recrystallization from ethanol/ethyl acetate, there is obtained 2-(3,4-dihydroxy-5-nitrophenyl)-4H-1-benzopyran-4-one in the form of yellow crystals of m.p. >240° (dec.).

EXAMPLE 65

a) 92 ml of n-butyl lithium solution (1.6M in hexane) are added dropwise at −70° within 20 minutes to 33.0 g of 4-bromobenzotrifluoride (dissolved in 150 ml of tetrahydrofuran). After stirring at −70° for 45 minutes, 36 g of 3-methoxy-4-benzyloxybenzaldehyde (dissolved in 100 ml of tetrahydrofuran) are added dropwise thereto at between −70° and −60°. The reaction mixture is stirred at −70° for 2 hours and at 0° for 1 hour, poured into a mixture of ice and 100 ml of 2N sulfuric acid and extracted twice with 500 ml of ether. The combined ether phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. There is obtained 4-(benzyloxy)-3-methoxy-4'-(trifluoromethyl)benzhydrol which can be used directly in the subsequent reaction step.

b) 52.6 g of 4-(benzyloxy)-3-methoxy-4'-(trifluoromethyl)benzhydrol (dissolved in 500 ml of methylene chloride) are treated within 10 minutes at 20° with 30.6 g of pyridinium chlorochromate and stirred at 20° for 2 hours. The precipitate formed is subsequently filtered and washed with methylene chloride. The filtrate is evaporated and the residue is chromatographed on 150 g of silica gel with methylene chloride. After recrystallization from methylene chloride/hexane, there is obtained 4-benzyloxy)-3-methoxy-4'-(trifluoromethyl)-benzophenone of melting point 101°.

c) 70 ml. of 33 percent hydrobromic acid in acetic acid are added within 15 minutes at 10° to 20 g of 4-(benzyloxy)-3-methoxy-4'-(trifluoromethyl)benzophenone (dissolved in 150 ml of methylene chloride). After

stirring at 20° for 1.5 hours, the reaction mixture is poured into 600 ml. of ice-water; the methylene chloride phase is separated and the aqueous phase is extracted twice more with 100 ml. of methylene chloride. The combined methylene chloride phases are washed with 600 ml of water, dried over sodium sulfate and evaporated. The residue is chromatographed on 150 g of silica gel with methylene chloride. After recrystallization from methylene chloride/hexane, there is obtained 4-hydroxy-3-methoxy-4'-(trifluoromethyl)benzophenone of melting point 97°.

d) 3.2 ml of 65 percent nitric acid are added dropwise within 10 minutes at 20° to 12.8 g of 4-hydroxy-3-methoxy-4'-(trifluoromethyl)benzophenone (dissolved in 160 ml of acetic acid). After stirring for 1.5 hours, the reaction mixture is poured into 600 ml of ice-water, and the precipitate formed is filtered off, washed with water and dissolved in methylene chloride. The methylene chloride solution is dried over sodium sulfate and evaporated, and the residue is recrystallized from methylene chloride/hexane. There is obtained 4-hydroxy-3-methoxy-5-nitro-4'-(trifluoromethyl)benzophenone of melting point 172°.

e) 2.0 g of 4-hydroxy-3-methoxy-5-nitro-4'-(trifluoromethyl)benzophenone (dissolved in 20 ml of 33 percent hydrobromic acid in glacial acetic acid) are stirred at 90° for 18 hours. Thereupon, 20 ml of 48 percent aqueous hydrobromic acid are added thereto, whereupon the mixture is stirred at 110° for an additional 18 hours. The reaction mixture is subsequently evaporated under reduced pressure and the residue is recrystallized from water. There is obtained 3,4-dihydroxy-5-nitro-4'-(trifluoromethyl)benzophenone of melting point 116°–118°.

EXAMPLE 66

a) 18.7 g of 4-hydroxy-3-methoxy-5-nitro-4'-(trifluoromethyl)benzophenone (dissolved in 250 ml of tetrahydrofuran) are treated at room temperature with 27.5 ml of 2N potassium hydroxide solution, whereupon the mixture is evaporated. The residue is treated with 200 ml of toluene, whereupon the mixture is again evaporated. Thereupon, the mixture is heated with 400 ml of toluene for 4 hours with the separation of water and under reflux. 100 ml of toluene are distilled and 10 ml of dimethylformamide and 20 ml of dimethyl sulfate (freshly distilled) are added, whereupon the mixture is heated under reflux for 5 hours. 300 ml of 1N sodium hydroxide solution are subsequently added at 20°. The reaction mixture is stirred for 30 minutes and treated with 200 ml of ether. The organic phase is separated; the aqueous phase is extracted twice more with 100 ml of ether; the combined ether phases are dried over sodium sulfate and evaporated, and the residue is chromatographed on 70 g of silica gel with methylene chloride. After recrystallization from methylene chloride/hexane there is obtained 3,4-dimethoxy-5-nitro-4'-(trifluoromethyl)benzophenone of melting point 115°.

b) 49.5 g of tin dichloride dihydrate are added to 16.0 g of 3,4-dimethoxy-5-nitro-4'-(trifluoromethyl)benzophenone (dissolved in 300 of ethanol), whereupon the mixture is stirred at 75° for 30 minutes. Thereupon, the reaction mixture is poured into 800 ml of ice-water. It is neutralized with 28 percent sodium hydroxide solution and extracted three times with 600 ml of methylene chloride. The combined methylene chloride phases are washed with water, dried over sodium sulfate and evaporated. After recrystallization from methylene chloride/hexane there is obtained 5-amino-3,4-dimethoxy-4'-(trifluoromethyl)benzophenone of melting point 95°–96°.

c) 3.25 g of 5-amino-3,4-dimethoxy-4'-(trifluoromethyl)-benzophenone (dissolved in 50 ml of acetone) are evaporated under reduced pressure after the addition of 15 ml of 2N sulfuric acid. The thus-obtained residue is suspended in 20 ml of acetic acid, diluted with 100 ml of water and treated at 5° with a solution of 700 mg of sodium nitrite in 10 ml of water. It is stirred at 5° for 1 hour. Thereupon, the diazonium salt solution is filtered, added at 5° to a solution of 2.0 g of sodium cyanide and 1.0 g of copper(I) cyanide in 20 ml of water and stirred at 5° for 1 hour. Thereupon, 200 ml of methylene chloride are added thereto. Insoluble constituents are filtered off. The phases are separated; the aqueous phase is extracted twice more with 100 ml of methylene chloride. The combined methylene chloride phases are washed with water, dried over sodium sulfate and evaporated. The residue is chromatographed on 30 g of silica gel with methylene chloride. After recrystallization from methylene chloride/hexane, there is obtained 5-cyano-3,4-dimethoxy-4'-(trifluoromethyl)benzophenone of melting point 130°.

d) 1.5 g 5-cyano-3,4-dimethoxy-4'-(trifluoromethyl)-benzophenone (dissolved in 75 ml of methylene chloride) are treated at 5° with 2.18 ml of boron tribromide, whereupon the mixture is stirred at room temperature for 18 hours. The reaction mixture is subsequently diluted with 50 ml of methylene chloride. The mixture is heated under reflux for an additional 4 hours, treated at −70° with 15 ml of methanol, stirred at room temperature for 2 hours, evaporated, the residue is dried in vacuo and partitioned between ethyl acetate and ice-water. The aqueous phase is extracted twice more with ethyl acetate. The combined ethyl acetate phases are dried over sodium sulfate and evaporated. The thus-obtained material is stirred at 130° for 6 hours with 10 ml of acetic anhydride and 1 ml of pyridine. The mixture is evaporated and the residue is partitioned between ice-water and methylene chloride. The methylene chloride phase is dried over sodium sulfate and evaporated, and the residue is chromatographed on 30 g of silica gel with methylene chloride. The thus-obtained diacetate is dissolved in 10 ml of methanol. The solution is treated with 4.2 ml of 1N sodium hydroxide solution, stirred at 0° for 1 hour, neutralized with acetic acid, evaporated and partitioned between ethyl acetate and saturated sodium chloride solution. The ethyl acetate phases are dried over sodium sulfate and evaporated, and the residue is recrystallized from methylene chloride. There is obtained 5-cyano-3,4-dihydroxy-4'-(trifluoromethyl)benzophenone of melting point 204°–206°.

In an analogous manner:

a1) From 2'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 3,4-dimethoxy-2'-fluoro-5-nitrobenzophenone of m.p. 86°–88° (from ether/low-boiling petroleum ether),

b1) from 3,4-dimethoxy-2'-fluoro-5-nitrobenzophenone there is obtained 5-amino-3,4-dimethoxy-2'-fluorobenzophenone of m.p. 93°–95° (from ether/low-boiling petroleum ether),

c1) from 5-amino-3,4-dimethoxy-2'-fluorobenzophenone there is obtained 5-benzoyl-2,3-dimethoxy-2'-fluorobenzonitrile of m.p. 132°–134° (from methylene chloride/low-boiling petroleum ether) and

d1) from 5-benzoyl-2,3-dimethoxy-2'-fluorobenzonitrile there is obtained 5-benzoyl-2,3-dihydroxy-2'-fluorobenzonitrile of m.p. 228°-230° (from ether/low-boiling petroleum ether).

In an analogous manner:

b2) from 3,4-dimethoxy-5-nitrobenzophenone there is obtained 5-amino-3,4-dimethoxybenzophenone as an amorphous solid,

c2) from 5-amino-3,4-dimethoxybenzophenone there is obtained 5-benzoyl-2,3-dimethoxybenzonitrile of m.p. 98°-100° (from ether/hexane) and

d2) from 5-benzoyl-2,3-dimethoxybenzonitrile there is obtained 5-benzoyl-2,3-dihydroxybenzonitrile of m.p. 212°-214° (from ethyl acetate/ether).

EXAMPLE 67

a) A solution of 16.0 g of 3,4-dimethoxy-5-nitrobenzoyl chloride in 80 ml of pyridine is added dropwise to a solution of 2.68 g of 1-methylimidazole and 6.6 g of triethylamine in 80 ml of pyridine, whereupon the mixture is stirred at 60° for 3 hours. After treatment with 1.70 ml of 3N sodium hydroxide solution the mixture is stirred for an additional 1 hour and subsequently poured into ice-water. The separated grey crystals are filtered under suction and taken up in ethyl acetate, whereupon the organic phase is dried over magnesium sulfate and the solvent is distilled. After recrystallization from ethyl acetate/hexane there is obtained 3,4-dimethoxy-5-nitrophenyl (1-emthylimidazol-2-yl) ketone in the form of colorless crystals of m.p. 144°-145°.

b) 5.0 g of 3,4-dimethoxy-5-nitrophenyl (1-methylimidazol-2-yl) ketone are treated with 50 ml of hydrobromic acid (48%), whereupon the mixture is stirred under reflux temperature for 2 hours. After cooling the separated precipitate is filtered under suction, washed with ice-water and recrystallized from ethanol. There is obtained 3,4-hydroxy-5-nitrophenyl (1-methylimidazol-2-yl) ketone hydrobromide in the form of yellow crystals of decomposition point >240°.

EXAMPLE 68

In analogy to Example 67, from 3,4-dimethoxy-5-nitrobenzoyl chloride and 1-benzylimidazole there is obtained 1-benzylimidazol-2-yl (3,4-dimethoxy-5-nitrophenyl) ketone in the form of colorless crystals of m.p. 134°-135° (from methylene chloride/hexane) and therefrom with hydrogen bromide there is obtained 1-benzylimidazol-2-yl (3,4-dihydroxy-5-nitrophenyl) ketone hydrobromide as yellow crystals of m.p. 218°-219° (dec.).

EXAMPLE 69

a) A solution of 10.0 g of 1-[(benzyloxy)-methyl-]imidazole in 50 ml of acetonitrile is added dropwise within 10 minutes while cooling with ice to a solution of 13.0 g of 3,4-dimethoxy-5-nitrobenzoyl chloride and 5.4 g of triethylamine in 80 ml of acetonitrile so that the temperature does not exceed 25°. The mixture is subsequently stirred for an additional 3 hours, whereupon the solvent is distilled. After treatment with water, the mixture is extracted with ethyl acetate. After two-fold washing with water, the organic phase is dried over sodium sulfate and evaporated. The resulting oil is chromatographed on 600 g of silica gel with toluene/ethyl acetate (95:5). There is obtained 1-[(benzyloxy)methyl-]imidazol-2-yl (3,4-dimethoxy-5-nitrophenyl) ketone as a yellowish oil

b) In analogy to Example 67b) there is obtained after treatment with hydrobromic acid 3,4-dihydroxy-5-nitrophenyl (imidazol-2-yl) ketone hydrobromide as yellow crystals of m.p. 247°-248°.

EXAMPLE 70

a) A solution of 25.0 g of 3-bromoquinoline is dissolved in 200 ml of dry ether and cooled to −60°. At this temperature there are added dropwise within 15 minutes 75.1 ml of a 1.6 molar solution of n-butyllithium, whereupon the mixture is stirred for 10 minutes. A solution of 26.5 g of vanillin benzyl ether in 250 ml of dry ether is added dropwise thereto at −60°, the mixture is subsequently stirred at room temperature of 3 hours, poured into about 1.5 l of ice-water and extracted three times with 600 ml of ethyl acetate each time. The organic phase is washed with water, dried over sodium sulfate and evaporated. The resulting oil is chromatographed on 1 kg of silica gel with methylene chloride-/ethyl acetate (1:1). The crystalline crude product obtained is recrystallized form ethyl acetate. There is obtained α-[4-(benzyloxy)-3-methoxyphenyl]-3-quinolinemethanol in the form of colourless crystals of m.p. 124°-125°.

b) A solution of 6.2 g of α-[4-(benzyloxy)-3-methoxyphenyl]-3-quinolinemethanol in 200 ml of methylene chloride is treated with 62 g of manganese dioxide and stirred at the reflux temperature 2 hours. After cooling the precipitate is filtered under suction and washed with methylene chloride. The filtrate is evaporated and the oil obtained is dissolved in hot ether, whereupon the solution is treated with a small amount of pentane. The separated crystals are filtered under suction. There is obtained 4-(benzyloxy)-3-methoxyphenyl (3-quinolinyl) ketone in the form of colorless crystals of m.p. 110°-111°.

c) 11.0 g of 4-(benzyloy)-3-methoxyphenyl (3-quinolinyl) ketone are treated with 50 ml of trifluoroacetic acid, whereupon the mixture is stirred at room temperature for 2 hours. After distillation of the trifluoroacetic acid, the residue is treated twice with 50 ml of ethanol each time and the solvent is distilled each time. The oil obtained crystallizes upon treatment with ethanol. After recrystallization from ethanol, there is obtained 4-hydroxy-3-methoxypyenyl (3-quinolinyl) ketone in the form of yellowish crystals of m.p. 196°-197°.

d) A solution of 1.91 ml of 65 percent nitric acid in 20 ml of glacial acetic acid is added dropwise to a solution of 5.5 g of 4-hydroxy-3-methoxyphenyl (3-quinolinyl) ketone in 300 ml of glacial acetic acid at 150° and the mixture is then stirred at this temperature for an additional 2 hours. The mixture is then poured into ice-water and extracted three times with 300 ml of ethyl acetate each time. The organic phase is washed five times with 100 ml of water each time, dried over sodium sulfate and evaporated. After treatment of the residue with ethyl acetate, there is obtained 4-hydroxy-3-methoxy-5-nitrophenyl (3-quinolinyl) ketone in the form of yellow crystals of m.p. 220°-221° (dec.).

e) 820 mg of 4-hydroxy-3-methoxy-5-nitrophenyl (3-quinolinyl) ketone are treated with 50 ml of 48 percent hydrobromic acid and held at the reflux temperature for 3 hours. After distillation of the hydrobromic acid at 50°, the residue is treated with 70 ml of hot water and the insoluble constituent is filtered under suction. There is obtained 3,4-dihydroxy-5-nitrophenyl (3-quinolinyl) ketone hydrobromide in the form of yellow crystals of m.p. 270° (dec.).

EXAMPLE 71

In analogy to Example 70 there is obtained α-[4-(benzyloxy)-3-methoxyphenyl]-4-quinolinemethanol as colorless crystals of m.p. 117°-118° (ethyl acetate), therefrom with manganese dioxide there is obtained 4-(benzyloxy)-3-methoxyphenyl (4-isoquinolinyl) ketone as colorless crystals of m.p. 126.5°-127.5°, therefrom with trifluoroacetic acid there is obtained 4-hydroxy-3-methoxyphenyl (4-isoquinolinyl) ketone as yellow crystals of m.p. 197.5°-198.5° and therefrom by nitration with nitric acid in glacial acetic acid and subsequent treatment with hydrobromic acid, there is obtained 3,4-dihydroxy-5-nitrophenyl (4-isoquinolinyl) ketone hydrobromide as yellow crystals of m.p. 256° (dec.).

EXAMPLE 72

In analogy to Example 70 there is obtained α-[4-(benzyloxy)-3-methoxyphenyl]-2-napthhalenemethanol as colorless crystals (ethyl acetate/hexane) of m.p. 113°-114°, therefrom with manganese dioxide there is obtained 4-(benzyloxy)-3-methoxyphenyl (2-naphthyl) ketone as colorless crystals (ethyl acetate/hexane) of m.p. 104°-105°, therefrom by treatment with trifluoroacetic acid and nitration with nitric acid in glacial acetic acid there is obtained 4-hydroxy-3-methoxy-5-nitrophenyl (2-nephthyl) ketone as yellow crystals of m.p. 187°-188° and therefrom by treatment with hydrobromic acid there is obtained 3,4-dihydroxy-5-nitrophenyl (2-naphthyl) ketone as yellow crystals of m.p. 814°-185°.

EXAMPLE 73

a) A solution of 20.0 g of 3-phenylpropyl bromide in 300 ml of ether is treated at −60° while stirring within 15 minutes with a solution of 71.8 ml of tert.butyllithium (1.4 molar) in pentane. After 10 minutes there is added dropwise at this temperature within 15 minutes a solution of 22.14 g of vanillin benzyl ether in 200 ml of ether, whereupon the mixture is stirred for an additional 2 hours. The mixture is poured into 1 l of ice-water and extracted three times with 500 ml of ethyl acetate each time. The organic phase is washed twice with 200 ml of water each time, dried over sodium sulfate and evaporated. The oil obtained is chromatographed on 1 kg of silica gel with methylene chloride. The crystals obtained are recrystallized from ether/pentane. There is obtained 4-(benzyloxy)-3-methoxy-α-(3-phenylpropyl)-benzyl alcohol in the form of colorless crystals of m.p. 71°-73°.

b) A solution of 9.0 g of 4-(benzyloxy)-3-methoxy-α-(3-phenylpropyl)benzyl alcohol in 250 ml of methylene chloride is treated with 90 g of manganese dioxide and held at the reflux temperature for 2 hours. After cooling, the precipitate is filtered under suction and washed with methylene chloride. The filtrate is evaporated and the residue is recrystallized from ethyl acetate/ether. There is obtained 4'-(benzyloxy)-3'-methoxy-4-phenylbutyrophenone in the form of colorless crystals of m.p. 81°-82°.

c) A solution of 7.0 g of 4'-(benzyloxy)-3'-methoxy-4-phenylbutyrophenone in 40 ml of 33 percent hydrobromic acid in glacial acetic acid is stirred at room temperature for 5 hours and subsequently poured into 500 ml of ice-water. The solution is adjusted to pH 6.0 by the addition of conc. ammonia and extracted three times with 250 ml of ethyl acetate each time. The organic phase is washed three times with 50 ml of water each time, dried over sodium sulfate and evaporated. The oil obtained is dissolved in 20 ml of ether, whereupon the solution is treated with hexane until it becomes turbin and is left to crystallize out. There is obtained colorless 4'-hydroxy-3'-methoxy-4-phenylbutyrophenone of m.p. 91°-92°.

d) A solution of 0.79 ml of 65 percent nitric acid in 25 ml of glacial acetic acid is added dropwise to a solution of 2.2 g of 4'-hydroxy-3'-methoxy-4-phenylbutyrophenone in 25 ml of glacial acetic acid and the mixture is stirred at room temperature for an additional 2 hours. The mixture is poured into 150 ml of ice-water and, after treatment with 20 ml of 3N hydrochloric acid, extracted three times with 75 ml of ethyl acetate each time. The organic phase is washed with water, dried over sodium sulfate and evaporated. The crude product obtained is taken up in ethyl acetate and filtered over 75 g of silica gel. After recrystallization from acetonitrile, there is obtained 4'-hydroxy-3'-methoxy-5'-nitro-4-phenylbutyrophenone in the form of yellow crystals of m.p. 120°-121°.

e) 1.0 g of 4'-hydroxy-3'-methoxy-5'-nitro-4-phenylbutrophenone is held at 200° for 1 hour with 8 g of pyridine hydrochloride. The reaction mixture is poured while still warm into ice-water and extracted with ethyl acetate. The organic phase is washed with 1N hydrochloric acid and subsequently with water, dried over sodium sulfate and evaporated. The dark residue obtained is chromatographed on a 30-fold amount of silica gel with ethyl acetate. From methylene chloride/hexane there is obtained 3',4'-dihydroxy-5'-nitro-4-phenylbutyrophenone in the form of yellow crystals of m.p. 118°-119°.

EXAMPLE 74

a) A solution of 14.68 g of potassium cyanide in 20 ml of water is added to a solution of 10.0 g of 3,4-dimethoxy-5-nitrobenzaldehyde in 100 ml of dioxane. 18.81 ml of 37 percent hydrochloric acid are now added dropwise thereto within 30 minutes while stirring vigorously. After the addition of 120 ml of ether, the excess hydrogen cyanide gas is driven off by passing argon through the mixture. The reaction mixture is filtered a siliceous earth filter aid, and the organic phase is washed with water dried over sodium sulfate and evaporated. The α-hydroxy-3,4-dimethoxy-phenylacetonitrile (yellowish oil) which is formed is dissolved in 200 ml of ether, whereupon the solution is treated with 20 ml of ethanol, cooled to 0° and hydrochloric acid gas is passed in for 30 minutes. After 3 hours, the separated colorless precipitate is filtered under suction and recrystallized from ethanol/ether. There is obtained ethyl (3,4-dimethoxy-5-nitrophenyl)hydroxy-acetimidate hydrochloride.

b) 19.7 g of ethyl (3,4-dimethoxy-5-nitrophenyl)hydroxyacetimidate are dissolved in 500 ml of ethanol. 6.73 g of o-phenylenediamine are added, the mixture is stirred at room temperature for 2 hours and subsequently held at the reflux temperature overnight. After distillation of the solvent, the residue is treated with 50 ml of water, made alkaline with sodium carbonate solution and extracted twice with 250 ml of methylene chloride each time. The organic phase is washed with water dried over sodium sulfate and evaporated. The orange residue obtained is chromatographed on 400 g of silica gel with methylene chloride/ethyl acetate (1:1). From ether/hexane there is obtained α-(3,4-dimethoxy-5

nitrophenyl)-2-benzimidazolemethanol in the form of yellowish crystals of m.p. 50° (dec.).

c) 13.2 g of α-(3,4-dimethoxy-5-nitrophenyl)-2-benzimidazolemethanol are dissolved in 200 ml of methylene chloride and, after treatment with 130 g of manganese dioxide, the mixture is stirred at the reflux temperature for 2 hours. After filtration, the solvent is distilled. There is obtained 2-benzimidazolyl (3,4-dimethoxy-5-nitrophenyl) ketone in the form of yellowish crystals of m.p. 212°–213°.

d) 1.0 g of 2-benzimidazolyl (3,4-dimethoxy-5-nitrophenyl) ketone and 8.0 g of pyridine hydrochloride are held at 200° for 60 minutes. The dark solution is poured while still warm into ice-water and extracted three times with 100 ml of ethyl acetate each time. The organic phase is washed with water, dried over sodium sulfate and evaporated. After recrystallization from ethyl acetate/hexane, there is obtained 2-benzimidazolyl (3,4-dihydroxy-5-nitrophenyl) ketone in the form of yellow crystals of m.p. 240°–250°.

EXAMPLE 75

a) 30.0 g of 3,4-dimethoxy-5-nitrobenzoic acid are dissolved in 250 ml of tetrahydrofuran and, after the addition of 21.85 g of 1,1'-carbonyldiimidazole, the mixture is stirred at the reflux temperature for 2 hours. The mixture is poured into 300 ml of ice-water and the precipitated crystals are filtered under suction after stirring for 30 minutes. The crystals are taken up in methylene chloride, whereupon the organic phase is washed with water, dried over sodium sulfate and evaporated. After crystallization from methylene chloride/-hexane, there is obtained 1-(3,4-dimethoxy-5-nitrobenzoyl)imidazole in the form of colorless crystals of m.p. 136°–137°.

b) 10.0 g of 1-(3,4-dimethoxy-5-nitrobenzoyl-)imidazole in 50 ml of dimethylformamide are treated with 6.95 g of acetamidoxime, whereupon the mixture is stirred at 70° for 1 hour. After cooling, the mixture is poured into 500 ml of ice-water and stirred for 30 minutes. The separated crystals are filtered under suction and washed with water. After crystallization from ethyl acetate there is obtained N'-[(3,4-dimethoxy-5-nitrobenzoyl)oxy]acetamidine in the form of colorless crystals of m.p. 165°–166°.

c) 2.0 g of N'-[(3,4-dimethoxy-5-nitrobenzoyl)oxy]acetamidine are held at reflux temperature for 1 hour in 20 ml of glacial acetic acid. After distillation of the acetic acid, the crystalline residue is recrystallized from ether/hexane. There is obtained 5-(3,4-dimethoxy-5-nitrophenyl)-3-methyl-1,2,4-oxadiazole in the form of colorless crystals of m.p. 111°.

d) 2.5 g of 5-(3,4-dimethoxy-5-nitrophenyl)-3-methyl-1,2,4-oxadiazole are dissolved in 70 ml of methylene chloride. After cooling to −60° there is added dropwise thereto within 20 minutes while stirring a solution of 23.62 g of boron tribromide in 50 ml of methylene chloride, whereupon the mixture is held at the reflux temperature for 48 hours. After cooling to −60°, the mixture is treated with 60 ml of ethanol and subsequently stirred at room temperature for 30 minutes. The yellow solution is evaporated to dryness, whereupon the residue is treated three times with 100 ml of toluene/ethanol (1:1) each time and the solvent is distilled each time. After crystallization from ethanol, there is obtained 5-(3-methyl-1,2,4-oxadiazol-5-yl)-3-nitropyrocatechol in the form of yellow crystals of m.p. 201°–202°.

EXAMPLE 76

a) 143.8 ml of n-butyllithium solution (1.53M in hexane) are added dropwise at −70° within 30 minutes to 35.0 g of 1-bromo-2-fluorobenzene (dissolved in 600 ml of tetrahydrofuran). After stirring at −70° for 60 minutes 48.5 g of 3-methoxy-4-benzyloxybenzaldehyde (dissolved in 450 ml of tetrahydrofuran) are added dropwise thereto during 30 minutes. The reaction mixture is stirred at −70° for 2 hours and at 0° for 30 minutes, poured into a mixture of ice and 150 ml of 2N sulfuric acid and extracted three times with 500 ml of ether. The combined ether phases are washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. There is obtained 4-(benzyloxy)-2'-fluoro-3'-methoxybenzhydrol as a yellowish oil which can be used directly in the subsequent reaction step.

In an analogous manner:

a1) From 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-3-fluorobenzene there is obtained 4-(benzyloxy-3'-fluoro-3-methoxybenzhydrol as an oil;

a2) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-4-fluorobenzene there is obtained 4-(benzyloxy)-4'-fluoro-3-methoxybenzhydrol as an oil;

a3) from 3-methoxybenzhydrol as an oil;

a4) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-2-chlorobenzene there is obtained 4-(benzyloxy)-2'-chloro-3-methoxybenzhydrol as an oil;

a5) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-3-chlorobenzene there is obtained 4-(benzyloxy)-3'-chloro-3-methoxybenzhydrol as an oil;

a6) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-4-chlorobenzene there is obtained 4-(benzyloxy)-4'-chloro-3-methoxybenzhydrol as an oil;

a7) from 4-benzyloxy-3-methoxybenzaldehyde and 2-bromotoluene there is obtained 4-(benzyloxy)-3-methoxy-2'-methylbenzhydrol as an oil;

a8) from 3-methoxy-4-benzyloxybenzaldehyde and 4-bromotoluene there is obtained 4-(benzyloxy)-3-methoxy-4'-methylbenzhydrol as an oil;

a9) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromobenzonitrile there is obtained 4-(benzyloxy)-2'-cyano-3-methoxybenzhydrol as an oil and

a10) from 3-methoxy-4-benzyloxybenzaldehyde and 1-bromo-2-trifluoromethylbenzene there is obtained 4-(benzlyoxy)-3-methoxy-2'-(trifluoromethyl)benzhydrol as an oil.

b) 69.8 g of 4-(benzyloxy)-2'-fluoro-3-methoxybenzhydrol (dissolved in 600 ml of methylene chloride) are treated within 30 minutes at 20° with 45.3 g of pyridinium chlorochromate and stirred at 20° for 3 hours. The precipitate formed is subsequently filtered and washed with methylene chloride. The filtrate is evaporated and the residue is filtered on 100 g of silica gel with ether. After recrystallization from ether, there is obtained 4-(benzyloxy)-2'-fluoro-3-methoxybenzophenone of m.p. 118°–120°.

In an analogous manner:

b1) From 4-(benzyloxy)-3'-fluoro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-3'-fluoro-3-methoxybenzophenone as an amorphous solid;

b2) from 4-(benzyloxy)-4'-fluoro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-4'-fluoro-3-methoxybenzophenone of m.p. 99°–101° (from ether/hexane);

b3) from 4-(benzyloxy)-2',6'-difluoro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-

difluoro-3-methoxybenzophenone of m.p. 139°-141° (from methylene chloride/ether);

b4) from 4-(benzyloxy)-2'-chloro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-2'-chloro-3-methoxybenzophenone of m.p. 128°-130° (from ether);

b5) from 4-(benzyloxy)-3'-chloro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-3'-chloro-3-methoxybenzophenone as an amorphous solid;

b6) from 4-(benzyloxy)-4'-chloro-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-4'-chloro-3-methoxybenzophenone of m.p. 106°-108° (from methylene chloride/hexane);

b7) from 4-(benzyloxy)-3-methoxy-2'-methylbenzhydrol there is obtained 4-(benzyloxy)-3-methoxy-2'-methylbenzophenone of m.p. 86°-88° (from isopropyl ether);

b8) from 4-(benzyloxy)-3-methoxy-4'-methylbenzhydrol there is obtained 4-(benzyloxy)-3-methoxy-4'-methylbenzophenone of m.p. 79°-81° (from ether/hexane);

b9) from 4-(benzyloxy)-2'-cyano-3-methoxybenzhydrol there is obtained 4-(benzyloxy)-2'-cyano-3-methoxybenzophenone as an amorphous solid and

b10) from 4-(benzyloxy)-3-methoxy-2'-(trifluoromethyl)benzyhydrol there is obtained 4-(benzyloxy)-3-methoxy-2'-(trifluoromethyl)benzophenone of m.p. 103°-105° (from ether).

c) 170 ml of 33 percent hydrobromic acid in glacial acetic acid are added at 20°-25° within 20 minutes to 42.4 g of 4-(benzyloxy)-2'-fluoro-3-methoxybenzophenone (dissolved in 450 ml of methylene chloride). After stirring at 20° for 1.5 hours, the reaction mixture is poured into 750 ml of ice-water; the methylene chloride phase is separated and the aqueous phase is extracted twice more with 200 ml of methylene chloride. The combined methylene chloride phases are washed with 1200 ml of water, dried over sodium sulfate and evaporated. In order to remove the resulting benzyl bromide, the oily residue is treated with hexane and decanted off. There is obtained 2'-fluoro-4-hydroxy-3-methoxybenzophenone as a yellowish oil which can be used directly in the subsequent reaction step.

In an analogous manner:

c1) From 4-(benzyloxy)-3'-fluoro-3-methoxybenzophenone there is obtained 3'-fluoro-4-hydroxy-3-methoxybenzophenone of m.p. 133°-135° (from methylene chloride/low-boiling petroleum ether);

c2) from 4-(benzyloxy)-4'-fluoro-3-methoxybenzophenone there is obtained 4'-fluoro-4-hydroxy-3-methoxybenzophenone of m.p. 139°-141° (from ether);

c3) from 4-(benzyloxy)-2',6'-difluoro-4-hydroxy-3-methoxybenzophenone of m.p. 130°-132° (from methylene chloride/low-boiling petroleum ether);

c4) from 4-(benzyloxy)-2'-chloro-3-methoxybenzophenone there is obtained 2'-chloro-4-hydroxy-3-methoxybenzophenone as an amorphous solid;

c5) from 4-(benzyloxy)-3'-chloro-3-methoxybenzophenone there is obtained 3'-chloro-4-hydroxy-3-methoxybenzophenone of m.p. 136°-138° (from methylene chloride);

c6) from 4-(benzyloxy)-4'-chloro-3-methoxybenzophenone there is obtained 4'-chloro-4-hydroxy-3-methoxybenzophenone of m.p. 114°-116° (from methylene chloride/low-boiling petroleum ether);

c7) from 4-(benzyloxy)-3-methoxy-2'-methylbenzophenone there is obtained 4-hydroxy-3-methoxy-2'-methylbenzophenone of m.p. 103°-105° (from isopropyl ether);

c8) from 4-(benzyloxy)-3-methoxy-4'-methylbenzophenone there is obtained 4-hydroxy-3-methoxy-4'-methylbenzophenone of m.p. 103°-105° (from ether/low boiling petroleum ether);

c9) from 4-(benzyloxy)-2'-cyano-3-methoxybenzophenone there is obtained 2'-cyano-4-hydroxy-3-methoxybenzophenone of m.p. 124°-126° from ether/n-hexane) and

c10) from 4-(benzyloxy)-3-methoxy-2'-(trifluoromethyl)benzophenone there is obtained 4-hydroxy-3-methoxy-2'-(trifluoromethyl)benzophenone of m.p. 115°-117° (from ether).

d) 7.8 ml of 65 percent nitric acid are added dropwise at 20° within 20 minutes to 29.4 g of 2'-fluoro-4-hydroxy-3-methoxybenzophenone (dissolved in 450 ml of acetic acid). After stirring for 1.5 hours, the reaction mixture is poured into 2 l of ice-water and the precipitate formed is filtered off, washed with water and dissolved in methylene chloride. The methylene chloride solution is washed with water, dried over sodium sulfate and evaporated. The residue is recrystallized from methanol. There is obtained 2'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 127°-129°.

In an analogous manner:

d1) From 3'-fluoro-4-hydroxy-3-methoxybenzophenone there is obtained 3'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 168°-170° (from methanol);

d2) from 4'-fluoro-4-hydroxy-3-methoxybenzophenone there is obtained 4'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 126°-128° (from ether);

d3) from 2',6'-difluoro-4-hydroxy-3-methoxybenzophenone there is obtained 2',6'-difluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 147°-149° (from methanol);

d4) from 2'-chloro-4-hydroxy-3-methoxybenzophenone there is obtained 2'-chloro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 123°-125° (from ether);

d5) from 3'-chloro-4-hydroxy-3-methoxybenzophenone there is obtained 3'-chloro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 152°-154° (from methanol);

d6) from 4'-chloro-4-hydroxy-3-methoxyphenone there is obtained 4'-chloro-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 128°-131° (from methylene chloride/low-boiling petroleum ether);

d7) from 4-hydroxy-3-methoxy-2'-methylbenzophenone there is obtained 4-hydroxy-3-methoxy-2'-methyl-5-nitrobenzophenone of m.p. 125°-127° (from ethanol);

d8) from 4-hydroxy-3-methoxy-4'-methoxybenzophenone there is obtained 4-hydroxy-3-methoxy-4'-methyl-5-nitrobenzophenone of m.p. 137°-139° (from methylene chloride/ether);

d9) from 2'-cyano-4-hydroxy-3-methoxybenzophenone there is obtained 2'-cyano-4-hydroxy-3-methoxy-5-nitrobenzophenone of m.p. 163°-164° (from methanol);

d10) from 4-hydroxy-3-methoxy-2'-(trifluoromethyl)benzophenone there is obtained 4-hydroxy-3-methoxy-5-nitro-2'-(trifluoromethyl)benzophenone of m.p. 138°-140° (from methylene chloride/low-boiling petroleum ether);

d11) from 4-hydroxy-3,4'-dimethoxybenzophenone there is obtained 4-hydroxy-3',4'-dimethoxy-5-nitrobenzophenone of m.p. 134°-136° (from methanol) and

d12) from 4-hydroxy-3,3',4'-trimethoxybenzophenone there is obtained 4-hydroxy-5-nitro-3,3',4'-trimethoxybenzophenone of m.p. 178°-180° (from methanol).

e) 24.8 g of 2'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone (dissolved in 120 ml of glacial acetic acid, 100 ml of 33 percent hydrobromic acid in glacial acetic acid and 68 ml of 48 percent aqueous hydrobromic acid) are boiled under reflux for 4 hours. The reaction mixture is subsequently evaporated under reduced pressure and the residue is distilled with toluene. The residue is dissolved in methylene chloride, washed with water, dried over sodium sulfate, filtered and evaporated. The product is crystallized from methylene chloride/low-boiling petroleum ether. There is obtained 2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 169°-171°.

In an analogous manner:

e1) From 3'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 3'-fluoro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 124°-126° (from methylene chloride);

e2) from 4'-fluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 4'-fluoro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 171°-173° (from methylene chloride);

e3) from 2',6'-difluoro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 2',6'-difluoro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 194°-196° (from methanol);

e4) from 2'-chloro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 2'-chloro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 129°-131° (from methylene chloride/low-boiling petroleum ether);

e5) from 3'-chloro-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 3'-chloro-3,4-dihydroxy-5-nitrobenzophenone of m.p. 143°-145° (from methylene chloride/low-boiling petroleum ether);

e6) from 4'-chloro-4-hydroxy-3-methoxybenzophenone there is obtained 4'-chloro-3,4-dihydroxybenzophenone of m.p. 174°-176° (from methylene chloride);

e7) from 4-hydroxy-3-methoxy-2'-methyl-5-nitrobenzophenone there is obtained 3,4-dihydroxy-2'-methyl-5-nitrobenzophenone of m.p. 164°-166° (from methylene chloride);

e8) from 4-hydroxy-3-methoxy-4'-methyl-5-nitrobenzophenone there is obtained 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone of m.p. 146°-148° (from methylene chloride);

e9) 2'-cyano-4-hydroxy-3-methoxy-5-nitrobenzophenone there is obtained 2'-cyano-3,4-dihydroxy-5-nitrobenzophenone of m.p. 159°-161° (from methanol);

e10) from 4-hydroxy-3-methoxy-5-nitro-2'-(trifluoromethyl)benzophenone there is obtained 3,4-dihydroxy-5-nitro-2'-(trifluoromethyl)benzophenone of m.p. 146°-148° (from methanol);

e11) from 4-hydroxy-3,4'-dimethoxy-5-nitrobenzophenone there is obtained 5-nitro-3,4,4'-trihydroxybenzophenone of m.p. 212°-214° (from methanol/-methylene chloride) and

e12) from 4-hydroxy-5-nitro-3,3',4'-trimethoxybenzophenone there is obtained 5-nitro-3,3',4,4'-tetrahydroxybenzophenone of m.p. 222°-224° (from ether).

EXAMPLE 77

A suspension of 13.8 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 9.0 g of 1-(phenethyl)-2-thiorea in 150 ml of n-butanol and the mixture is heated to boiling under reflux for 3 hours. After cooling to room temperature, the crystals are filtered under suction and crystallized from n-butanol. There is obtained 3-nitro-5-[2-(phenethylamino)-4-thiazolyl]-pyrocatechol hydrobromide of m.p. 249°-251°.

EXAMPLE 78

In analogy to Example 38, from 2-bromo-3',4'-dihydroxy-5'-nitroacteophenone and 2-aminobenzophenone there is obtained 2-(3,4-dihydroxy-5-nitrobenzoyl)-3-phenylindole of m.p. 196°-198° (from isopropanol).

EXAMPLE 79

A suspension of 8.3 g of 2-bromo-3',4'-dihydroxy-5'-nitroacetophenone is treated with 1-(1-adamantyl)-2-thiourea in 90 ml of n-butanol and the mixture is heated to boiling under reflux for 4 hours. After cooling to room temperature, the crystals are filtered under suction and recrystallized from n-butanol. There is obtained 5-[2-(1-adamantylamino)-5-thiazolyl]-3-nitropyrocatechol hydrobromide of m.p. 245°-247°.

EXAMPLE 80

A suspension of 2.6 g of (3,4-dihydroxy-5-nitrobenzoyl)methyl acetate in 20 ml of ethanol and 20 ml of 1N hydrochloric acid is heated to boiling under reflux for 5 hours. The reaction mixture is then evaporated, the residue is distilled with toluene and then recrystallized from ethanol. There is obtained 2,3',4'-trihydroxy-5'-nitroacetophenone of m.p. 208°-210°.

EXAMPLE 81

A solution of 4.0 g of n-hexyl 3,4-dihydroxy-5-nitrophenylglyoxylate and 1.5 g of diaminomaleonitrile in 35 ml of ethanol is heated to boiling under relfux for 24 hours. The alcohol is then distilled, the residue is dissolved in ether, washed with water, dried over sodium sulfate, filtered and evaporated. There is obtained 6-hydroxy-5-(3,4-dihydroxy-5-nitrophenyl)-2,3-pyrazinedicarbonitrile of m.p. >300° (from ether/-methylene chloride).

EXAMPLE 82

a) 4.2 g of 5-(bromoacetyl)-2,3-dimethoxybenzonitrile dissolved in 150 ml of methylene chloride are treated with 8.9 ml of boron tribromide. The reaction mixture is stirred at 20° for 18 hours. It is subsequently poured into 220 ml of saturated sodium hydrogen carbonate solution and 100 g of ice, adjusted to pH 6 with glacial acetic acid and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and evaporated. There is obtained 5-(bromoacetyl)-2,3-dihydroxybenzonitrile as an amorphous solid.

b) 3.8 g of 5-(bromoacetyl)-2,3-dihydroxybenzonitrile dissolved in 25 ml of N,N-dimethylformamide are treated with N-phenylthiourea and stirred at 100° for 5 hours. Thereafter, the solvent is removed by evaporation. The residue is treated with 200 ml of 1N sodium carbonate solution and extracted three times with 100 ml of methylene chloride each time. The combined organic phases are washed with water, dried over sodium sulfate and evaporated. The residue is chromatographed on 30 g of silica gel with ethyl acetate. The thus-obtained crude product is treated with 40 ml of 1N hydrochloric acid, evaporated and crystallized from acetone. There is obtained 5-(2-anilino-4-thiazolyl)-2,3-dihydroxybenzonitrile hydrochloride of m.p. 245°-247°.

EXAMPLE 83

a) 25 ml of tert.-butylithium solution (1.4M in hexane) are added dropwise at −70° within 10 minutes to 10 g of 4-benzyloxy)-3-methoxy-bromobenzene dissolved in 100 ml of tetrahydrofuran. After stirring at −70° for 1 hour, 5 g of quinoline-4-carbaldehyde dissolved in 50 ml of tetrahydrofuran are added dropwise within 30 minutes. The reaction mixture is stirred at −40° for 1 hour and at −5° for 1 hour, poured into 200 ml of water and adjusted to pH 4 with glacial acetic acid. The mixture is extracted three times with 50 ml of ether each time. The combined ether phases are washed with water, dried over sodium sulfate and evaporated. There is obtained α-[4(benzyloxy)-3-methoxyphenyl]-4-quinolinemethanol as an amorphous solid.

b) 9.4 g of α-[4-(benzyloxy)-3-methoxyphenyl]-4-quinolinemethanol dissolved in 200 ml of methylene chloride are treated with 6.5 g of pyridinium chlorochromate, whereupon the mixture is stirred at room temperature for 3 hours. The insoluble constituents are subsequently filtered off. The filtrate is evaporated and the residue is chromatographed on 150 g of silica gel with ethyl acetate. There is thus obtained 4-(benzyloxy)-3-methoxyphenyl 4-quinolyl ketone as an amorphous solid.

c) 15 ml of 33 percent hydrobromic acid in glacial acetic acid are added dropwise within 5 minutes at room temperature to 7.5 g of 4-(benzyloxy)-3-methoxyphenyl 4-quinolyl ketone dissolved in 150 ml of methylene chloride. After stirring at 20° for 4.5 hours, the reaction mixture is poured portionwise into 250 ml of saturated sodium bicarbonate solution. The methylene chloride phase is separated; the aqueous phase is extracted twice with 100 ml of methylene chloride each time. The combined methylene chloride phases are dried over sodium sulfate and evaporated. The residue is recrystallized from methylene chloride/hexane. There is obtained 4-hydroxy-3-methoxyphenyl 4-quinolyl ketone of m.p. 190°–192°.

d) 0.37 ml of 65 percent nitric acid is added dropwise at room temperature to 1.3 g of 4-hydroxy-3-methoxyphenyl 4-quinolyl ketone. After stirring for 3 hours the reaction mixture is poured into ice-water, adjusted to pH 6 with conc. ammonia and the precipitate formed is filtered. The thus-obtained residue is heated under reflux in 20 ml of acetonitrile, whereupon the crystals are filtered at 0°. There is obtained 4-hydroxy-3-methoxy-5-nitrophenyl 4-quinolyl ketone of m.p. 246°–248°.

e) 1g of 4-hydroxy-3-methoxy-5-nitrophenyl 4-quinilyl ketone dissolved in 30 ml of 48 percent aqueous hydrobromic acid is stirred at 100° for 18 hours. After cooling to room temperature, the reaction mixture is diluted with 30 ml of water and the precipitate is filtered under suction. There is obtained 3,4-dihydroxy-5-nitrophenyl 4-quinolyl ketone hydrobromide of m.p. 273°–275° (from acetonitrile).

EXAMPLE 84

a) 18.8 ml of n-butyllithium solution (1.6M in hexane) are added dropwise at −50° within 10 minutes to 4.03 g of thiophene dissolved in 40 ml of tetrahydrofuran. After stirring at −50° for 30 minutes 6.3 g of 3,4-dimethoxy-5-nitrobenzaldehyde dissolved in 100 ml of tetrahydrofuran are added dropwise within 30 minutes. The reaction mixture is stirred at −50° for 1 hour at 0° for 30 minutes and poured into 100 ml of 2N sulphuric acid. The mixture is extracted three times with 100 ml of ether each time; the combined ether phases are washed with sodium chloride solution, dried over sodium sulfate, filtered and evaporated. There is obtained α-(3,4-dimethoxy-5-nitrophenyl)-2-thiophenemethanol of m.p. 79°–81° (from methylene chloride/hexane).

b) 9.9 g of α-(3,4-dimethoxy-5-nitrophenyl)-2-thiophenemethanol dissolved in 300 ml of acetone are treated with 90 g of manganese dioxide and heated under reflux for 4 hours. The manganese dioxide is removed by suction filtration and the filtrate is evaporated. There is obtained 3,4-dimethoxy-5-nitrophenyl 2-thienyl ketone of m.p. 102°–104° (from methylene chloride/hexane).

c) 2 g of 3,4-dimethoxy-5-nitrophenyl 2-thienyl ketone are stirred at 100° for 8 hours in a mixture of 20 ml of 30–33 percent hydrobromic acid in glacial acetic acid and 20 ml of 48 percent aqueous hydrobromic acid. The reaction mixture is subsequently evaporated to dryness. The residue is taken up in ethyl acetate, washed with water, dried over sodium sulfate and filtered, and the filtrate is evaporated. After recrystallization from ethyl acetate/hexane there is obtained 3,4-dihydroxy-5-nitrophenyl 2-thienyl ketone of m.p. 155°–157°.

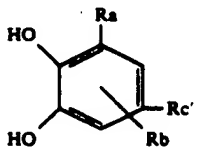
EXAMPLE A

The interlocking gelatine capsules of the following composition can be prepared in a known manner:

Ingredients	Amount in mg/capsules
L-Dopa	100
Benserazide hydrochloride	29.3
3,4-Dihydroxy-5-nitrophenyl 4-pyridyl ketone	25
Gelatine	1
Magnesium stearate	1
Avicel	93.7
Mannitol	100
Capsule fill weight	350 mg

We claim:

1. A compound of the formula



Ib

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc' is the group CO—R^{11} wherein R^{11} is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl, or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof.

2. A compound, according to claim 1, wherein Rb is situated in the p-position to Ra.

3. A compound, according to claim 2, wherein Ra is nitro.

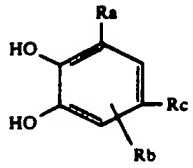
4. A compound, according to claim 3, wherein Rb is hydrogen, chlorine or fluorine.

5. A compound, according to claim 4, wherein Rb is hydrogen.

6. A compound, according to claim 1, 3,4-Dihydroxy-5-nitrobenzophenone.

7. A compound, according to claim 1, 2'-Fluoro-3,4-dihydroxy-5-nitrobenzophenone.

8. A pharmaceutical composition comprising a compound of the formula

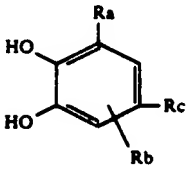


wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is CO—R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl or an ester or ether derivative thereof which if hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

9. A pharmaceutical composition, according to claim 8, wherein the compound of formula Ia is 3,4-dihydroxy-5-nitrobenzophenone.

10. A pharmaceutical composition, according to claim 8, wherein the compound of formula Ia is 2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone.

11. A pharmaceutical composition comprising L-dopa, peripheral decarboxylase inhibitor, a compound of the formula



wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is the group CO—R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier material.

12. A pharmaceutical composition, according to claim 11, wherein the compound of formula Ia is 3,4-dihydroxy-5-nitrobenzophenone.

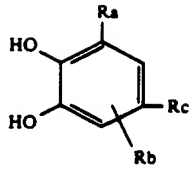
13. A pharmaceutical composition, according to claim 11, wherein the compound of formula Ia is 2'-fluoro-3,4-dihydroxy-5-nitrobenzophenone.

14. A compound according to claim 1, wherein said compound is 4-dihydroxy-5'-methyl-5-nitrobenzophenone.

15. A pharmaceutical composition according to claim 8, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

16. A pharmaceutical composition according to claim 11, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

17. A pharmaceutical composition for treating depression comprising an effective amount of a compound of the formula

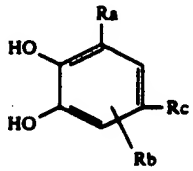


Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is CO—R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl or an ester or ether derivative thereof which if hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

18. A pharmaceutical composition according to claim 17, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

19. A pharmaceutical composition for treating Parkinson's disease comprising L-dopa, a peripheral decarboxylase inhibitor, a compound of the formula

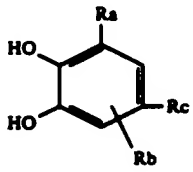


Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is CO—R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl or an ester or ether derivative thereof which if hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

20. A pharmaceutical composition according to claim 19, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

21. A pharmaceutical composition for inhibiting catechol-O-methyl-transferase, said composition comprising a catechol-O-methyl transferase inhibiting amount of a compound of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is CO—R^1 wherein R^1 is a phenyl group optionally mono- or disubstituted by halogen, cyano, hydroxy or lower alkyl or an ester or ether derivative thereof which if hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

22. A pharmaceutical composition according to claim 8, wherein the compound of formula Ia is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

4

PATENT NO. : 5,236,952
DATED : August 17, 1993
INVENTOR(S) : Karl Bernauer, Janos Borgulya, Hans Bruderer, Mose PaPrada, Gerhard Zurcher

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

- Claim 14, Column 61, lines 54-55: "4-dihydroxy-5'-methyl - 5-nitrobenzophenone should read --- 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone --- .

Signed and Sealed this
Ninth Day of May, 1995

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

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5

PAYOR NUMBER
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75N4

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY NJ 07110

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,236,952	183	1020	----	07/686,210	08/17/93	04/16/91	04	NO	PAID

file

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Department PLP

FEB 7 1997
PATENT LAW

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM
NBR

1

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV 4-88)

Roche Pharmaceuticals
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-235-5005

(6)

October 29, 1990

Central Document Room
Center for Drugs and Biologics
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

Ladies and Gentlemen:

Re: Investigational New Drug Application
Ro 40-7592, Oral
Serial Submission No. 000

Pursuant to Section 505(i) of the Federal Food, Drug and Cosmetic Act and Section 312.20 of Title 21 of the Code of Federal Regulations, we herewith submit, in triplicate, an Investigational New Drug Application for Ro 40-7592 for oral administration. Ro 40-7592 will be studied under this IND for the oral treatment of Parkinson's disease.

Ro 40-7592 (COMT Inhibitor) may be a useful addition to the current therapy of Parkinson's disease. It is very likely that fluctuations in therapeutic response currently observed with Sinemet® are at least in part related to rapid methylation of L-dopa by COMT. These fluctuations could be significantly diminished if methylation of L-dopa were blocked.

Non-U.S. IND studies are underway in Europe. Our initial protocol under this IND, Protocol N3565B, will assess the tolerability of increasing single doses of Ro 40-7592 when given together with Sinemet® 25/100 mg to healthy volunteers.

This IND submission consists of ten volumes and an overall table of contents is attached.

We understand that this Investigational New Drug Application and all information contained therein, unless otherwise made by public by Hoffmann-La Roche Inc. is CONFIDENTIAL. Additionally, certain pages herein are marked "CONFIDENTIAL" because the information therein constitutes trade secrets or information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552) and would remain so subsequent to approval of an NDA for this drug. If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials marked CONFIDENTIAL should be made to any member of the public, we expect that because of the importance of maintaining confidentiality of these materials to Hoffmann-La Roche Inc. you will first consult with us on the issue of disclosure.

If you have any questions regarding this IND, please contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Senior Regulatory Specialist
Drug Regulatory Affairs

AJC:kt
Attachments

HLR No. 90-1129

INVESTIGATIONAL NEW DRUG APPLICATION

Ro 40-7592 (COMT Inhibitor) Oral

OVERALL TABLE OF CONTENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
Hoffmann-La Roche Inc.

2. DATE OF SUBMISSION
October 29, 1990

3. ADDRESS *(Number, Street, City, State and Zip Code)*
340 Kingsland Street
Nutley, New Jersey 07110

4. TELEPHONE NUMBER *(Include Area Code)*
(201) 235-5005

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Ro 40-7592 3,4 Dihydroxy-4'-methyl-5-nitrobenzophenone

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Anti Parkinson's

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

Hoffmann-La Roche Inc., Type I, Master File 301

10. SERIAL NUMBER: **0 0 0**

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☐ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED
PLEASE SEE VOLUME 10 FOR COMPLETE DATA.		DIVISION ASSIGNMENT

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE

AJC:CAS
HLR No. 90-1129

Central Document Room
Center for Drugs and Biologics

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- [X] 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- [X] 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- [X] 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- [X] 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X]* d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- [X] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - [X] a. Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- [X] 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- [X] 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- [ ] 10. Additional information *[21 CFR 312.23 (a) (10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [X] YES [ ] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [ ] YES [X] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Grzegorz S. Sedek, M.D., Ph.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Grzegorz S. Sedek, M.D., Ph.D.

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND or on earlier notification by FDA. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Anthony J. Corrado Drug Regulatory Affairs	Anthony J. Corrado	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110	(201) 235-5005	10/29/90

(**WARNING**: A willfully false statement is a criminal offense U S C Title 18. Sec. 1001.)

U.S. GPO: 1987 .0- 18 44452

(7)

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3724
Fax (201) 812-3700/3554

June 3, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

Ladies and Gentlemen:

Re: NDA 20-697
TASMAR™ (tolcapone) Tablets
Original New Drug Application

Introduction:

In accordance with 21 CFR Part 314.50, we are submitting a New Drug Application for the use of TASMAR (tolcapone) tablets in the treatment of fluctuating and non-fluctuating patients with Parkinson's Disease. In this patient population, TASMAR is intended for use as an adjunct to levodopa/carbidopa therapy.

Tolcapone is an orally active, potent, selective and reversible catechol-0-methyltransferase (COMT) inhibitor. Administered concomitantly with levodopa and an aromatic amino acid decarboxylase (AADC) inhibitor (carbidopa or benserazide), it leads to more stable plasma levels of levodopa by reducing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD). This leads to an improvement in symptomatic response and may allow a reduction of the daily dose of levodopa.

Therapeutic Clinical Program:

Clinical studies in the U.S. investigated the use of TASMAR coadministered with Sinemet (levodopa/carbidopa) while non-U.S. IND studies investigated the use of TASMAR administered concomitantly with either Sinemet or Madopar (levodopa/benserazide). Madopar is not commercially available in the U.S.

The safety and efficacy of TASMAR have been substantiated by the results of the following adequate and well-controlled therapeutic trials which were conducted under IND 35,698.

- Protocol NZ14316 - Double-blind, placebo-controlled, parallel groups, multicenter, dose-finding evaluation of Ro 40-7592 in parkinsonian patients under chronic treatment with Sinemet (levodopa/carbidopa) and presenting with end-of-dose wearing off.

- Protocol NZ14654 - Double-blind, placebo-controlled, parallel-groups, multicenter evaluation of tolcapone when given together with Sinemet (levodopa/carbidopa) to Parkinson's patients who exhibit end-of-dose wearing-off.

- Protocol NZ14971 - Double-blind, placebo-controlled, parallel-groups, multicenter evaluation of the marketing formulation of tolcapone when given together with Sinemet (levodopa/carbidopa) to Parkinson's disease patients who exhibit end-of-dose wearing-off.

- Protocol NZ14653 - Evaluation of the efficacy and safety of tolcapone in Parkinson's disease patients with a stable response to Sinemet (levodopa/carbidopa).

In addition to the results of the above mentioned U.S. IND studies, results from the following non-U.S. IND studies also substantiate the efficacy and safety of TASMAR.

- Protocol BZ14114 - Double-blind, placebo-controlled, parallel groups, multicenter dose finding study of Ro-40-7592 in patients pre-treated with standard Madopar or Sinemet (ratio 4:1) and presenting with "wearing-off" phenomenon.

- Protocol BZ14115 - Influence of the addition of Ro-40-7592 (200 mg and 400 mg t.i.d.) on to Madopar or Sinemet (ratio 4:1) dose regimen in parkinsonian patients. Double-blind, placebo-controlled, parallel groups followed by a crossover, multicenter study.

- Protocol NZ14655 - Double-blind, placebo-controlled, parallel-groups, multicenter, evaluation of tolcapone when given together with Madopar (levodopa/benserazide) to Parkinson's patients who exhibit end-of-dose wearing-off.

The following open-label, active-controlled, comparative trial, conducted in France, demonstrated that TASMAR in combination with Sinemet or Madopar therapy was more effective than the dopamine agonist, bromocriptine:

- NZ14656 - Open label, randomized, exploratory study comparing tolcapone to bromocriptine in Parkinson's patients treated with Madopar or Sinemet and with predictable "on/off" fluctuations.

In addition to the data from the above mentioned controlled clinical studies this application also contains results from the following uncontrolled studies:

- Protocol NZ14657 - Open-label, long-term evaluation of the safety of tolcapone in Parkinson's disease patients on levodopa containing therapy.

- Open-label extensions to protocols NZ14316, BZ14114, BZ14115 and NZ14656.

Safety Database:

A total of 2839 patients and volunteers have participated in TASMAR's global clinical development program, with 2327 receiving at least one dose of TASMAR. Of 1934 Parkinson's patients who participated in the therapeutic studies, 1536 received TASMAR.

Certain study extensions in the TASMAR clinical development program were ongoing beyond the point of the NDA clinical cut-off. Safety information collected after the NDA clinical cut-off will be included in the 4-month safety update.

FDA/Roche Meetings:

The TASMAR NDA incorporates various suggestions made by the Division at our January 23, 1995 End-of-Phase II meeting, March 15, 1995 Biopharmaceutic meeting, December 12, 1995 Pre-NDA CMC Meeting and our February 15, 1996 Pre-NDA Clinical meeting.

NDA Organization:

This application consists of 620 volumes. An Overall Table of Contents and complete Index are located in Volume one. The following is a brief description of each section:

The NDA is organized as follows:	Volume(s)
Section 1 - Index	1
Section 2 - Summary	2
Section 3 - Chemistry, Manufacturing and Controls	3-11
Section 4 - Samples, Methods Validation and Labeling	12-14
Section 5 - Nonclinical Pharmacology and Toxicology	15-88
Section 6 - Human Pharmacokinetics and Biopharmaceutics	89-164
Section 8/10 - Clinical and Statistical	165-335
Section 11 - Case Report Tabulations	336-419
Section 12 - Case Report Forms	420- 620

NDA Referencing System:

Each document in Section 5, 6 and 8/10 has a unique reference number. The referencing system for these sections is outlined below. To determine the volume location of a particular reference please refer to the Index located in volume one.

Section 5: Non-clinical Pharmacology and Toxicology

Reference #

1000 = Toxicology Summary
2000 = Preclinical Pharmacology Summary
3000 = Preclinical Pharmacokinetic Summary
6000 = Analytical Methods Summary

1001-1087 = Toxicology study reports and publications
2001-2120 = Preclinical Pharmacology study reports and publications
3001-3041 = Preclinical Pharmacokinetic study reports and publications
6001-6032 = Analytical Methods study reports and publications

Section 6: Human Pharmacokinetics and Biopharmaceutics

Reference #

4100 = Human Pharmacokinetics and Biopharmaceutics Summary
6000 = Analytical Methods Summary
4001-4069 = Clinical Pharmacology study reports and publications
6001-6032 = Analytical Methods study reports and publications

Section 8/10: Clinical/Statistical

Reference #
4000 = Clinical Pharmacology Summary
5000 = Benefit/Risk Statement
5200 = Integrated Efficacy Summary
5300 = Integrated Safety Summary/Drug Abuse and Overdose Statement
4001-4069 = Clinical Pharmacology study reports and publications
5001-5031 = Clinical study reports and publications

CANDA:

As agreed upon at the Pre-NDA meeting (February 15, 1996), the TASMAR CANDA will be submitted after the submission of the paper NDA. We anticipate the delivery of the CANDA, on a mutually acceptable date, approximately 45 days after the submission of the paper NDA.

Chemistry, Manufacturing and Controls (CMC):

Section 3 of this NDA provides the CMC information for tolcapone drug substance and TASMAR tablets. Tolcapone is synthesized in Basel, Switzerland by F. Hoffmann-La Roche and Company, Ltd. The tolcapone drug substance is milled at a milling site, operated by F. Hoffmann-La Roche and Company, Ltd., located in Basel, Switzerland. TASMAR tablets are manufactured in Nutley, New Jersey by Hoffmann-La Roche Inc.

Drug Master Files:

The letters of authorization for the Drug Master Files referenced in this NDA follow this letter. Please note that copies of these letters are also located in Section 3 of this application.

Field Office Copy:

In conformance with 21 CFR 314.71(b), we certify that an identical copy of section 3 of this application, which provides the chemistry, manufacturing and controls information for tolcapone drug substance and TASMAR tablets, has been provided to the home district office at the address below. A copy of the cover letter which accompanied this information follows this letter.

Ms. Regina Brown
Pre-Approval Program Manager
Food and Drug Administration
120 North Central Drive
North Brunswick, NJ 08902

Patent Information:

Following this letter is patent information on the drug (U.S. Patent No. 5,236,952) and method of use (U.S. Patent No. 5,467,875) for TASMAR (tolcapone).

User Fee:

Following this letter is a copy of our check for the User Fee payment for this NDA and a copy of the cover letter which accompanied our payment.

Confidentiality:

Information and data submitted herein contain trade secret or confidential information which is the property of Hoffmann-La Roche Inc. The Food and Drug Administration is not authorized to disclose this information or data to any member of the public without written permission from Hoffmann-La Roche.

Roche Contacts:

Please contact Ms. Virginia Pate at (201) 812-3550 with any chemistry, manufacturing and controls issues and Mr. Thomas Watson at (201) 812-3724 for all other issues.

Sincerely,

HOFFMANN-LA ROCHE INC.

Thomas J. Watson
Manager
Drug Regulatory Affairs

and

Virginia A. Pate
Manager
Drug Regulatory Affairs

TJW/gsm
Attachments
HLR No. 1996-1085

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314)

Form approved : OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Hoffmann-La Roche Inc.	June 3, 1996
ADDRESS *(Number, Street, City, State, and Zip Code)*	TELEPHONE NO. (Include Area Code)
340 Kingsland Street Nutley, New Jersey 07110-1199	(201) 812-3724
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* NDA 20-697

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
tolcapone	TASMAR

CODE NAME (If any)	CHEMICAL NAME
Ro 40-7592	3,4-dihydroxy-4'-methyl-5-nitrobenzophenone

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Tablets	Oral	100&200mg

PROPOSED INDICATIONS FOR USE

Parkinson's Disease

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND 35,698 - tolcapone, Hoffmann-La Roche Inc.
DMF 3696 - FMC Corporation
DMF 721 - Colorcon
DMF 1466 - Wheaton Plastic Products
DMF 1016 - Phillips Chemical Company
DMF 1646- Chevron
DMF 1362 - Solvay Polymers
DMF 1186 - Paxon Polymer Company
DMF 4428 - Ferdinand Gutmann & Co.
DMF 8362 - Ironwood Industries, Inc.
DMF 8168 - Ironwood industries Inc.
DMF 4164 - American White Cross
DMF 2880 - United Desiccants
DMF 7377 - Multiform Desiccants, Inc.
DMF 932 - Grace Davison
DMF 885 - Quantum

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
X	2. Summary (21 CFR 314.50(c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Thomas J. Watson, Manager, DRA	Thomas J. Watson	6/3/96
ADDRESS *(Street, City, State, Zip Code)* Hoffmann-La Roche Inc. 340 Kingsland Street, Nutley, NJ 07110-1199		TELEPHONE NO *(Include Area Code)* (201) 812-3724

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

EXHIBIT 8

TASMAR® TABLETS

TESTING PHASE - IND 35,698

COMMUNICATION	DATE OF COMMUNICATION
Original IND/Information/Protocol Amendment	10/29/90
FDA Letter - Acknowledging receipt of IND	11/9/90
Telephone Call - advising Roche to proceed with initial study and advising Roche to address points raised by FDA before proceeding with additional studies	12/19/90
Telephone Call - FDA letter regarding concerns to be addressed prior to initiation of additional studies not yet sent	1/28/91
Information Amendment - Pharmacology/Toxicology	3/11/91
Information Amendment - chemistry	3/11/91
Request for Information - FDA letter commenting on clinical protocol, toxicology and CMC data included in the original IND. Prior to initiation of Phase II clinical trials FDA requested additional non-clinical characterization of tolcapone when administered with Sinemet® (carbidopa/levadopa)	5/30/91
*Information Amendment - Protocol Amendment	5/31/91
#Telephone Call - Request for written submission for a meeting to discuss requests in 5/30/91 FDA letter	6/14/91
#General Correspondence - Response to 5/30/91 FDA letter, submitting information requested on toxicology data and clinical tiral data	6/28/91
#Telephone Call - discussions regarding request for further clarification of toxiclogical, pharmacalogical, and matters cited in FDA letter dated May 30, 1991	7/11/91
#Telephone Call - Call to FDA. FDA stated that review process not yet complete, but FDA expects to have questions regarding toxicology and pharmacology	8/13/91
#Telephone Call - FDA requests clarification of toxicology and pharmacology issues	8/28/91
#Information Amendment - Response to FDA request, chemistry	8/30/91
#Telephone Call - Regarding 6/28/91 submission which provided toxicology and clinical trial data	9/6/91
#FDA Meeting - Inquiry as to whether FDA reviewing pharmacologist responded to toxicology/pharmacology questions	10/3/91
*Protocol Amendment - New protocol, new investigator	10/4/91
#Telephone Call - FDA pharmacologist will not be able to	10/17/91

respond to toxicology/pharmacology questions in reasonable period of time	
*Information Amendment - Pharmacology/toxicology	10/21/91
*Information Amendment - Pharmacology/toxicology, clinical	11/18/91
#Telephone Call - Clarifying documentation needed in support of proposal to conduct Phase II clinical studies	11/22/91
#Information Amendment - Pharmacology/Toxicology, providing two study proticol outlines for toxicological and pharmacological animal intraction studies, characterizing tolcapone in combination with Sinemet	12/6/91
*Information Amendment - Pharmacology/toxicology, clinical	12/19/91
*Annual Report	12/20/91
*Protocol Amendment - New protocol, new investigator	12/20/91
#Telephone Call - Inquiry as to status of Information Amendment providing two study protocol outlines for toxicological and pharmacological animal interaction studies, characterizing tolcapone in combination with Sinemet	1/7/92
#General Correspondence and Information Amendment - submitting new clinical information available from European Phase I studies and published literature which have direct bearing on initiation of Phase II clinical trials	3/13/92
*Information Amendment - Pharmacology/Toxicology, clinical	3/18/92
*Information Amendment - Chemistry	3/19/92
*Information Amendment - New protocol, new investigator, clinical, chemistry	3/26/92
*Protocol Amendment - Change in protocol	3/30/92
*Protocol Amendment and Information Amendment - New protocol, new investigator, clinical	4/8/92
#General Correspondence - Provided preclinical data requested in 5/30/91 FDA letter and additional data to support initiation of Phase II clinical trials #Information Amendment - Pharmacology/Toxicology - progress reports on 4-week oral toxicity study with tolcapone with carbidopa/levadopa in rats and cynomologous monkeys #Information Amendment - clinical - blinded safety data from two Phase I studies #General Correspondence - Draft protocol synopsis of Phase II study	9/16/92
#Telephone Call - Discussed initiating Phase II clinical trials and status of review of results of preclinical data submitted with General Correspondence dated 9/16/92	11/23/92

#General Correspondence- Regarding initiating Phase II clinical trials including draft Phase II protocol #Information Amendment - Pharmacology/Toxicology Response to FDA Request	12/23/92
*Information Amendment - Pharmacology/Toxicology, clinical	1/14/93
*Annual Report Information Amendment - Clinical, Chemistry	2/1/93
#Telephone Call - FDA approval for initiation of Phase II clinical trials	3/1/93
Information Amendment - Protocol Amendment	3/26/93
Information Amendment - Protocol Amendment	5/5/93
Information Amendment - Clinical	7/9/93
Information Amendment - Pharmacology/Toxicology	7/23/93
Protocol Amendment - New Investigator, Change in Protocol	8/9/93
Information Amendment - Pharmacology/Toxicology	10/11/93
Information Amendment - Clinical, Chemistry Protocol Amendment - Change in protocol	10/21/93
Information Amendment - Clinical	11/5/93
IND Safety Report - Initial written report - adverse event	11/11/93
IND Safety Report - Preclinical Safety Report - coadminstration with ketamine	12/23/93
Information Amendment - New investigator, chemistry Protocol Amendment - New protocol	1/12/94
Annual Report	2/4/94
Protocol Amendment - New Investigator, change of address	2/18/94
Information Amendment - New Protocol, new investigator Protocol Amendment - Clinical, chemistry	3/31/94
IND Safety Report - Initial Written Report - adverse event	4/25/94
Protocol Amendment - Change in protocol, new investigator	5/16/94
IND Safety Report - Initial Written Report - adverse event	7/6/94
IND Safety Report - Initial Written Report - adverse event	7/6/94
IND Safety Report - Initial Written Report - adverse event	7/20/94
Telephone Call - Discussion with FDA of blinding issues	6/29/94
IND Safety Report - Initial Written Report - adverse event	8/1/94
IND Safety Report - Initial Written Report - adverse event	8/1/94
IND Safety Report - Initial Written Report - adverse event	8/1/94
Protocol Amendment - Change in protocol	8/12/94
Information Amendment - Pharmacology/Toxicology, clinical	8/16/94
Request for Information - FDA letter c12/23/92 correspondence	8/16/94
Information Amendment - Chemistry	9/1/94
Information Amendment - Clinical, Request for end of Phase II	9/9/94

meeting with FDA	
IND Safety Report - Initial Written Report - adverse event	9/16/94
Information Amendment - Pharmacology/Toxicology	10/4/94
IND Safety Report - Initial Written Report - adverse event	10/6/94
Information Amendment - Clinical	10/17/94
IND Safety Report - Initial Written Report - adverse event	10/27/94
Protocol Amendment - New protocol, new investigator	10/28/94
Response to FDA Request - Combination Segment II studies for combination with Sinemet in women of childbearing years Information Amendment - Pharmacology/Toxicology	11/4/94
Information Amendment - FDA meeting to request withdrawal of 9/9/94 Information Amendment; Information Amendment - Clinical	11/7/94
Information Amendment - Clinical FDA Meeting - Request for end of Phase II meeting to gain concurrence on suitability of clinical development plan	11/8/94
Telephone Call - Request for further information regarding adverse event	11/4/94
Telephone Call - Request for Information - 3-day report regarding adverse event	11/16/94
Protocol Amendment - New investigator, change of investigator	11/18/94
Information Amendment - Clinical IND Safety Report and Response to FDA Request - Follow-up to a Written Report	11/22/94
Information Amendment - Protocol Amendment, change in protocol, chemistry	12/9/94
Information Amendment - Chemistry Protocol Amendment - New protocol, new investigator	1/9/95
General Correspondence - FDA Meeting - Agenda for End of Phase II meeting	1/16/95
Annual Report	1/27/95
Information Amendment - Chemistry Protocol Amendment - New protocol, new investigator,	2/8/95
Protocol Amendment - New protocol, new investigator	2/24/95
Protocol Amendment - Change in protocol	2/27/95
FDA Meeting - End of Phase II Meeting with FDA; Tolcapone Development Plan for Parkinson's Disease	1/23/95
Response to FDA Request - desk copy of 2/8/95 Amendment	3/8/95
Protocol Amendment - New protocol, new investigator	3/21/95
Telephone Call - informing FDA of clerical error in a previous submission	4/5/95
IND Safety Report - Initial Written Report - adverse event	4/5/95

General Correspondence - Proposals in response to statistical recommendations	4/6/95
Information Amendment - Clinical, chemistry Protocol Amendment - New investigator, Change in protocol	4/13/95
Information Amendment - Clinical	5/8/95
General Correspondence - Minutes of End of Phase II Meeting on Tolcapone development for Parkinson's Disease	5/17/95
Protocol Amendment - Change in protocol	6/2/95
Telephone Call - Discussing patient request to receive tolcapone	6/27/95
General Correspondence - Information on pharmacokinetics	6/27/95
Information Amendment - Clinical	6/28/95
Protocol Amendment - New investigator, change in protocol	7/26/95
Response to FDA request - trade name	8/15/95
IND Safety Report - Initial Written Report - adverse event	8/21/95
Telephone Call - Discussion of primary efficacy variables	9/11/95
Telephone Call - Discussion of TASMAR CADNA	9/12/95
General Correspondence - FDA Meeting - biopharmaceutical meeting	10/10/95
Protocol Amendment - New protocol, new investigator	10/25/95
Telephone Call - addressing various issues	10/25/95
General Correspondence - Meeting to discuss CMC section of NDA	11/8/95
Telephone Call - Discussing pre-NDA meeting issues	11/28/95
Information Amendment - Clinical	12/1/95
IND Safety Report - Initial Written Report - adverse event	12/8/95
IND Safety Report - Initial Written Report - reporting findings in 2 year carcinogenicity study in rats	12/19/95
Information Amendment - Clinical	12/20/95
General Correspondence - pre-NDA meeting request package	12/21/95
Protocol Amendment - New investigator, change of address	12/21/95
FDA Pre-NDA meeting CMC meeting	1/18/96
IND Safety Report - Initial Written Report - adverse event	1/24/96
Annual Report	1/29/96
Protocol Amendment - Change in protocol	2/2/96
General Correspondence - Pre-NDA meeting information, amending pooling strategy	2/6/96
Information Amendment - Pharmacology/Toxicology	2/9/96
General Correspondence - Pre NDA CMC meeting minutes	2/14/96
General Correspondence - Minutes for Pre-NDA meeting for TASMAR/Parkinson's Disease	3/12/96
Follow-Up Safety Report - follow up to 12/23/93 Preclinical Safetry Report discussing coadminstration with ketamine	3/20/96

Information Amendment - Pharmacology/Toxicology	
Telephone Call - Discussion of Tolcapone dissolution test method	3/20/96
FDA Letter - Pre-NDA meeting minutes	4/25/96
Protocol Amendment - New protocol, new investigators	5/30/96
Protocol Amendment - New investigators Information Amendment - Clinical	6/25/96
Protocol Amendment - Change in protocol, new investigators	8/7/96
Protocol Amendment - Change in protocol	10/8/96
Information Amendment - CMC, revisions to test specifications and directions for testing	10/9/96
Protocol Amendment - New Investigators	11/7/96
Authorization Letter - Authorized reference to IND for a third party IND	12/4/96
Authorization Letter - Authorized reference to IND for a third party IND	12/4/96
Protocol Amendment - New Investigator	12/5/96
Information Amendment - CMC	12/11/96
Protocol Amendment - Change in protocol	12/12/96
Annual Report	1/28/97
Protocol Amendment - New protocol, new investigators	3/17/97
Protocol Amendment - Change in protocol, new investigator	4/24/97
Protocol Amendment - New investigators	5/16/97
Protocol Amendment - New Investigators	6/2/97
Protocol Amendment - New Investigators	6/16/97
Protocol Amendment - New protocol	7/11/97
Protocol Amendment - New protocol, new investigators	8/6/97
Protocol Amendment - New Investigators	8/16/97
IND Safety Report - Initial Written Report - adverse event	8/28/97
Information Amendment - CMC, chemistry, microbiology	9/12/97
Protocol Amendment - New investigators	9/23/97
Protocol Amendment - New investigators	10/21/97
IND Safety Report - Initial Written Report - adverse events	11/3/97
IND Safety Report - Initial Written Report - adverse events	11/25/97
Protocol Amendment - New investigator, change of principal investigators	12/8/97
Protocol Amendment - New investigator	12/19/97
Protocol Amendment - Change in protocol	1/13/97
IND Annual Report	1/15/98
IND Safety Report - Follow-up to an initial written report (11/3/97 and 11/25/97 IND Safety Reports)	1/20/98

* - Relates to Phase I clinical trial

- Relates to initiation of Phase II clinical trial

TASMAR® TABLETS

APPLICATION PHASE - NDA 20-697

COMMUNICATION	DATE OF COMMUNICATION
Original NDA - TASMAR Tablets for treatment of fluctuating and non-fluctuating patients with Parkinson's Disease	6/3/96
General Correspondence - Field copy of cover letter, completed Form 365H, Section 2 (Application Summary), and Section 3-A and 3B (CMC - Drug Substance and Drug Product	6/3/96
FDA Letter - Acknowledging receipt of Original NDA	6/17/96
Telephone Call - Discussion of assignment of medical reviewer	6/24/96
NDA Amendment - Carcinogenecity data and SAS data sets and analysis programs	6/26/96
FDA Letter - Suggestions for electronic submission of NDA to Neuropharmacological Drug Products	6/27/96
NDA Amendment - Provided electronic files of population pharmacokinetic NONMEM data sets	7/10/96
Telephone Call - Discussion of TASMAR CANDA	7/10/96
General Correspondence - Notice of intent to provide CANDA System	7/23/96
FDA Letter - Requests from FDA reviewing pharmacologist regarding non-clinical toxicology studies	8/8/96
NDA Amendment - Provided animal data requested in FDA	8/29/96
FDA Letter - Requests from FDA reviewing pharmacologist related to two year rat carcinogenicity study	9/9/96
NDA Amendment - Provided animal data requested in FDA Letter of 8/8/96	9/9/96
General Correspondence - Provided disks as an update to TASMAR CANDA	9/11/96
NDA Amendment - Provided clinical information requested by FDA Clinical Investigations Branch	9/16/96
NDA Amendment - Provided fax of data sets for protocols	9/17/96
NDA Amendment - Response to FDA's request for patient diary SAS sets on diskette	9/23/96
NDA Amendment - Provided toxicology information in response to FDA requests	9/25/96
FDA Letter - Requests from reviewing pharmacologist regarding submission if non-clinical data	9/26/96

General Correspondence - Four month safety update	10/3/96
NDA Amendment - Provided toxicology information requested by FDA	10/8/96
General Correspondence - Provided clinical information requested by Clinical Investigations Branch	10/9/96
NDA Amendment - Response to FDA request for clarification regarding 2 year mouse carcinogenicity study	10/25/96
Telephone Call - FDA request for additional statistical analysis of UPDRS measures	11/6/96
General Correspondence - Inspectional observations	11/13/96
NDA Amendment - Response to FDA request for case report forms	11/18/96
NDA Amendment - Response to FDA request for additional statistical analysis	11/19/96
NDA Amendment - Provided test specifications and directions for testing for the drug product	11/20/97
FDA Letter - FDA provided a copy of the environmental assessment deficiencies for TASMAR NDA	12/4/96
NDA Amendment - CMC revisions to drug substance section of the NDA	12/17/96
NDA Amendment - Response to FDA request for Environmental Assessment information	1/7/97
NDA Amendment - CMC - Jaycap Closure to be used with opaque high-density polyethylene bottle used in packaging TASMAR	2/14/97
NDA Amendment - Response to FDA request for urine analysis measurements	2/24/97
General Correspondence - Response to FDA request for information on use in clinical trial of clinical trial formulation vs. marketing formulation	3/5/97
NDA Amendment - CMC, addition of alternate milling facility	3/10/97
NDA Amendment - CMC, additional dissolution information in response to Biopharmaceutical reviewers	3/21/97
General Correspondence - Response to FDA request providing total tolcapone exposure up to 4 month safety update, NDA and 4 month safety update cutoff, comparison of clinical and marketing formulation, adverse events	4/14/97
General Correspondence - Response to FDA request providing safety analysis comparing clinical and marketing formulations, European Union Summary of Product Characteristics, and Swiss Prescribing Information	4/25/97
NDA Amendment - CMC, revising manufacture of drug to	4/30/97

incorporate use of activated carbon in final purification step	
General Correspondence - Field copy of amendment to NDA, containing CMC information regarding use of activated carbon in final purification	4/30/97
FDA Letter - FDA Inspection - recommendation that NDA be placed in an approvable status	5/30/97
FDA Letter - FDA completed review of NDA and considers it approvable. Issues of chemistry, biopharmaceutics and clinical to be discussed. Requested safety update and introductory promotional material	6/5/97
General Correspondence - Notified FDA of plan to file amendment containing responses to issues raised in approvable letter	6/13/97
General Correspondence - Market Exclusivity Information	7/15/97
NDA Amendment - Response to approvable letter/redraft of labeling/Twelve month safety update	7/28/97
NDA Amendment - Provision of full reference with respect to previous NDA Amendment	7/30/97
FDA Letter - Acknowledgment of receipt of previous NDA Amendments, containing clinical information in response to approvable letter	8/12/97
General Correspondence - Cutoff plans for 4 month safety update and 12 month safety update	9/2/97
Telephone Call - Explanation of efficacy table values presented in package insert derivation	9/12/97
Telephone Call - Ascertaining TASMAR review status	9/29/97
General Correspondence - Return of TASMAR CANDA	9/29/97
General Correspondence - Disk of efficacy tables	9/29/97
Telephone Call - Response to medical reviewer question	10/7/97
Telephone Call - Ascertaining when FDA would send next draft of package insert	10/7/97
Telephone Call - Proposing amendment to NDA, providing for an extension of the expiration dating period without impacting User Fee clock	10/14/97
NDA Amendment - CMC, revision of proposed expiration dating period, change in fill count of proposed market package, stability data supporting revisions	10/21/97
Telephone Call - indication of possible approval in January, 1998 unless there are significant labeling issues	11/7/97
NDA Amendment - alternative draft labeling to be used on bottle cap	12/5/97

FDA Letter - Communication regarding advertisement	1/12/98
FDA Letter - Proposed draft labeling	1/15/98
General Correspondence - Response to FDA communication regarding advertising	1/22/98
General Correspondence - Request for FDA review of a draft press release announcing approval of TASMAR	1/26/98
FDA Letter - FDA approval of TASMAR tablets	1/29/98
FDA Letter - amended FDA approval letter	1/30/98

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